DECEMBER 1956
VOL. XIV NO. 6

Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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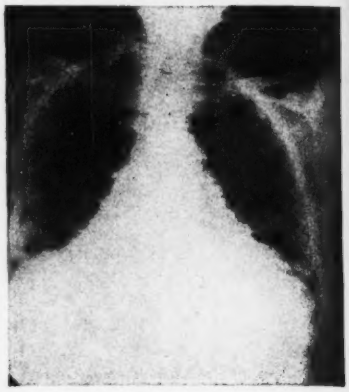

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1. Abramson, Julius; Brezniek, Elliott; and Sapienza, P.L.: *New England Jour. Med.*, 243:44, July 13, 1950.
2. Conybeare, John; and Mann, W.N.: Textbook of Medicine. Edinburgh, E. & S. Livingstone Ltd., 10th ed., 1952, p. 443.

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Editorial

Hyponatremia: Clinical State or Biochemical Sign?

IN THIS age of chemistry and of nuclear physics the increasing complexity of diagnostic technics does not necessarily lead immediately to simplification of physiologic and clinical problems. In no situation is this more evident than in that of patients suffering from certain disorders of water and electrolyte distribution that are characterized by hyponatremia, a lower-than-normal concentration of sodium in plasma. This single biochemical sign, a measurement of concentration only, has been interpreted enthusiastically to indicate a variety of physiologic disturbances with which indeed the term seems to have become synonymous. The result has been confusion, a confusion in part of terminology and in part of physiologic understanding and therapeutic indication. The extent of this uncertainty is indicated by the number of recent excellent and well-documented reviews of the problem (each one containing a slightly different classification)[1-8] as well as by the motivation to write this editorial. My purpose, however, is not to propound the answers but rather to clarify the problems, semantic, physiologic, and therapeutic, that sooner or later present themselves to every physician in the practice of medicine.

Hyponatremia, and especially the associated hypochloremia, early were recognized as signs of depletion of sodium and other extracellular electrolytes in many clinical situations, such as those involving abnormal losses of gastrointestinal fluids, diabetic ketosis, adrenocortical insufficiency, and certain types of renal disease. This sign was likewise regularly produced by experimental procedures designed to remove sodium from the body. Hyponatremia and hypochloremia have also been known for a long time to accompany certain states of excessive hydration. So far, so good, for the observed change in plasma concentration of sodium was readily interpreted in simple terms in respect to the whole body: too little salt or too much water.

However, the situation did not remain simple for long. Over the past decades edematous patients undergoing repeated treatment with mercurial diuretics have been observed to exhibit, on occasion, a rapid deterioration of circulatory and renal function.[9-14] This state was found to be associated with a depressed concentration of sodium in serum, and from this association was born that enigmatic and contentious term, *the low-salt syndrome*.[15] The rapid development of flame photometry quickly established hyponatremia to be a not infrequent biochemical sign in such patients wrung dry by the overenthusiastic use of diuretic measures or in patients whose edema had become obstinately refractory to conventional forms of therapy.[16-21] Nor did the results of the ubiquitous, if not indiscriminate, measurement of serum sodium levels stop there. It was soon appreciated that many chronically ill patients, with and without edema, were hyponatremic and were adamant in their resistance to the endeavors of the therapist to restore the aberrant dimension to his preconceived ideas of physiologic normality.[13, 19, 22] Patients with normal or excess stores of sodium clearly contained water in even greater excess of at least that portion of the body sodium that was in aqueous solu-

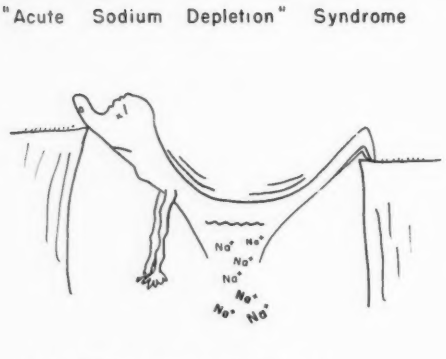

FIG. 1. This is treatable—if caught in time

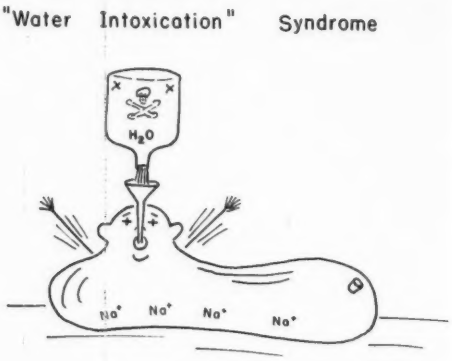

FIG. 2. This is avoidable

tion;[23-25] and their regulatory mechanisms were subverted to the maintenance of this distorted relationship, although for the whole body the excess of sodium was greater than that of water. Thus, the etiologic significance of hyponatremia became more and more befogged, although all too clear was its prognostic significance as a hallmark of impending dissolution.

Despite the fact that the semantic difficulties concerning these hyponatremic states are inherently bound up with the difficulties of physiologic interpretation, they warrant some preliminary consideration. The term *low-salt syndrome* is hard to define. Substitution of *sodium* for *salt* does not help very much, for we still do not know whether the sodium is low in respect to normal amounts of the ion in all or some parts of the body or merely is low in relation to water. Should this term be applied to hyponatremic patients who have edema, or who have just been freed from edema, or who have not had any edema? As originally used by Schroeder,[15] "low-salt syndrome" applied to those patients on prolonged therapy with mercurial diuretics and a low-sodium diet who developed all the signs of acute sodium depletion shock and who responded to hypertonic solutions of sodium chloride. More recently, as the number of hyponatremic patients who are unresponsive to such treatment has increased, the term has been extended to patients whose primary difficulties are more closely related to excess of water than to total or systemic deficit of sodium. In view of its ambiguities, therefore, this term could well be dropped despite its common usage. *Hyponatremic states* is a term that has been widely employed.[6] It is merely descriptive, however, of the biochemical sign common to a number of clinical states that differ greatly in their pathophysiology and hence is useful only as a generic term. *Sodium paradox* has been applied[4, 25] to those hyponatremic states in which an excess of total body sodium is accompanied by a low extracellular concentration of the ion; this term underscores our ignorance but does not define wherein lies the paradox. *Dilution syndrome* has found its adherents[1, 2] and clearly emphasizes the role of abnormal retention of water. It applies more logically to simple water excess. *A new steady state*[8] properly stresses the disturbed regulatory mechanisms, but has a thermodynamic meaning that is by no means restricted to the situation under discussion. Considering the multiplicity of these terms and their general unsatisfactoriness, it is apparent that identification of physiologic mechanisms is a prerequisite to adequate nomenclature.

The clinical states characterized by the sign of hyponatremia constitute a spectrum of physiologic disturbances. The 2 ends of this spectrum, as indicated above, have been long and clearly recognized, namely, absolute deficit of sodium and absolute excess of water.

In *absolute sodium depletion* of the total o

g nism the factors of general and renal circulato y failure[26-28] lead to the clinical signs of s ock: tachycardia, hypotension, oliguria, and a otemia; such patients go to pieces rapidly (f g. 1). When these signs occur in conjunction w th a fairly rapid and progressive fall of the s um sodium concentration over a period of a f w days in a patient with edema of his lower e tremities or with ascites, it is well to consi er that "systemic" sodium depletion has o curred. This means an absolute deficit of s dium in the circulating plasma and interstitial fluid in which sodium is freely exchangeable and transportable despite the presence of pools of interstitial or ascitic fluid where sodium and water are segregated. This is the type of case that was first described as the low-salt syndrome and that is most likely to respond to treatment with hypertonic solutions of sodium chloride (if properly given).

The physiologic and clinical consequences of an *absolute excess of water* consist of cellular overhydration, pulmonary edema, restlessness, mental confusion, and convulsions.[5, 29, 30] Hence the synonym, *water intoxication*. Its biochemical sign likewise is hyponatremia. Its pathogenesis lies in the administration of water in amounts exceeding the organism's ability to excrete it (fig. 2) and it usually is produced iatrogenically in the oliguric phase of acute renal failure,[31] in renal failure due to circulatory inadequacy,[32] and in the antidiuretic phase of the postoperative period.[33, 34]

Between these 2 ends of the spectrum lies a series of disturbances that perhaps are well designated by the term *sodium-water disproportion*. These states might also be called *relative dilution hyponatremia* or *dysnatremia*; further descent into the depths of Latin and Greek for such a satisfying philologic mouthful as *hydronatriodyskinesis* is more likely to produce consternation than clarification. Whatever the label, water exceeds the stores of osmotically active sodium, which in turn may be high or low; edema may or may not be present. Techniques of dilution of the radioisotopes of sodium and measurement of total body water have elucidated the body composition in these conditions.[23-25] Such studies indicate that the total exchangeable sodium in the body may be in excess of normal although the concentration of the ion in extracellular fluid is low. The degree of excess of sodium and water may be masked by variation in body fat content, but in relation to lean body mass both of these constituents of the body fluids are often present in excessive amounts.

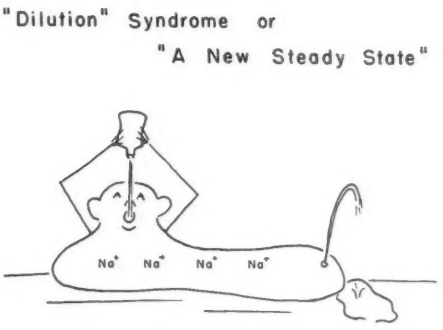

FIG. 3. This requires therapeutic restraint

Two separate but related groups of factors appear in the pathogenesis of this abnormal situation. The first group consists of *regulatory factors* that permit the maintenance of a new abnormal steady state (fig. 3) in which: (A) the total content of osmotically active solutes is low in relation to the total water content, and (B) the total body content of solutes, especially sodium, is increased. The first factor, A, must involve a new "set" to the receptors that regulate water intake (thirst) and water excretion (Verney's osmoreceptors controlling the production of antidiuretic hormone). This receptor-effector mechanism regulates the amount of water in the body in relation to the total quantity of osmotically active solute, i.e., total osmolar concentration. The second factor, B, must involve the as-yet-undefined receptor-effector mechanism that controls the solute, or at least the sodium, load of the body and hence the total volume of extracellular fluid. There is good evidence, as well as *a priori* reasons, for these related regulatory mechanisms being involved in the clinical states under consideration.[1, 12, 21, 35, 36] Hyponatremic cardiacs cannot excrete a standard water load despite a further fall in extracellular osmolar

concentration[36, 37] and serum antidiuretic activity is increased under these circumstances;[36] these responses are opposite to those found in the normal subject in whom a water load has caused a drop in serum osmolar concentration, and are the same as those observed in hyponatremic patients with adrenocortical insufficiency.[36] Furthermore, the administration to hyponatremic edematous patients of alcohol, an agent known to inhibit the release of antidiuretic hormone, may on occasion produce a true water diuresis with correction of the hyponatremia[38] although failure to obtain such a result with any consistency indicates that other factors may be paramount.[39] In the main, however, these observations suggest that the secretion of antidiuretic hormone may be stimulated by an abnormality of volume rather than of total osmolar concentration. Change in some function of volume may also affect the renal tubular reabsorption and excretion of sodium, possibly through the adrenal cortex. Recent experimental evidence suggests that secretion of adrenocortical steroids may be abnormally stimulated in congestive heart failure[40-42] and it is of interest that one of the most important of these in respect to mineral metabolism, aldosterone, is sensitive to changes in certain parameters of body fluid volume as well as to change in total cationic load.[43, 44] The state of adrenocortical activity in the hyponatremic edematous patient, however, is quite uncertain at present; it has even been claimed recently that adrenal exhaustion accounts for the antidiuresis and for its amelioration by treatment with corticotropin or cortisone.[45] The experimental literature concerning the mechanisms regulating volume and osmolar concentration of the body fluids is so extensive that it will not be further elaborated upon here, since it has been reviewed elsewhere.[35, 46-48]

The second group of factors may be classified as *cellular*, and consist (A) of decreased osmotic activity of cellular solutes (cellular hypo-osmolarity), (B) of internal shifts and segregation of sodium, and (C) of fatigue of the metabolic sodium pump or of those mechanisms that depend on oxidative energy to maintain the differential distribution of ions across the cell boundary. Cellular hypo-osmolarity, A, has been postulated to occur under many experimental and clinical conditions.[3] Such a mechanism would readily explain an altered relationship between intracellular volume and external osmolar concentration in an osmoreceptor cell. I have already speculated in detail in the pages of this journal on the possible role of this factor in the "set" of the antidiuretic hormone and thirst receptors.[5] Internal shifts of sodium, B, frequently may be involved, but it is naive to consider that a fall in extracellular sodium concentration could result merely from transfer of sodium ion into the intracellular fluid. As long as cell boundaries are freely permeable to water no change in extracellular sodium concentration would take place; the cation must become osmotically inactivated within the cell or segregated out of aqueous solution in some other large depot such as bone. Reciprocal transfers of potassium, as demonstrated by Laragh,[49] can play a part only insofar as they contribute to changes in the total pool of osmotically active cations in solution; repletion of a potassium deficit in a hypokalemic patient may "displace intracellular" sodium and have a dramatic effect on obliterating an associated hyponatremia.[49, 50] Finally, C, fatigue of the cellular mechanism for maintaining a low concentration of sodium inside the cell (sodium pump) and a high concentration of potassium outside the cell has been emphasized, especially by Moore,[4] as the explanation of persistent hyponatremia and hyperkalemia in many patients with acute or chronic illnesses. This has been called *adaptation hyponatremia*[4, 7] but might be more succinctly described as *the tired cell syndrome* (fig. 4). It is difficult, however, to believe that cellular factors *alone* could result in this electrolytic pattern without concomitant failure of regulatory and of renal function. But the concept does serve to underscore the multiple factors and basic processes that may be involved in severely ill patients and that are indicated by the biochemical sign of hyponatremia.

The clinical setting for these patients with sodium-water disproportion or the relative dilution syndrome is primarily that of chron-

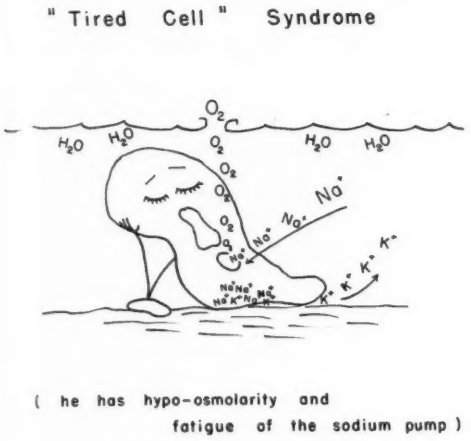

FIG. 4. This calls for a tonic

debilitating disease with malnutrition. Such diseases include tuberculosis,[51-55] intracranial tumors,[56, 57] hypopituitarism,[58] anorexia nervosa,[59] undernutrition,[24, 60] cirrhosis,[61-63] and many types of cardiovascular and renal disorders. Recent studies of patients with cardiac disease before and after valvulotomy have been especially revealing in respect to this syndrome.[64-66] They have shown a hyponatremia due to postoperative retention of water superimposed on an already high sodium content of the body, an abnormality that disappears over time with the recovery of cardiac function. The manner in which all these disease states result in the aberrations of regulatory and metabolic function, as outlined, is by no means adequately understood. Nevertheless, this group of hyponatremic states presents a different therapeutic problem from the hyponatremic patients suffering predominantly from acute total or "systemic" sodium depletion with its circulatory sequelae. It is not always easy to separate these 2 groups prior to therapy; yet the correct treatment is the most pressing problem before the physician.

Let us face the fact quite frankly that therapy of the hyponatremic patient more often than not is a shot in the dark, a matter of trial and error. This is especially true, since the several types may be mixed to varying degrees in the same patient. If acute systemic sodium depletion is suspected to be a predominant factor, administration of hypertonic solutions of sodium salts should be given an adequate trial. The reaction against such therapy has gone to an unwarranted extreme, in my opinion. Often it has been unsuccessful because of failure to limit rigidly the concurrent intake of water, and because of failure to recognize that for this brief period thirst will be a trying but necessary symptom. But where uncertainty exists as to the role of sodium depletion in the hyponatremic still-edematous patients who have become unresponsive to mercurial diuretics, a more conservative set of therapeutic trials is indicated. The refractory effect of mercurial-induced hypochloremic metabolic alkalosis is well recognized[67] and warrants alternation with acidifying agents such as ammonium chloride and carbonic anhydrase inhibitors, given separately or together.[68] Indeed, the use of this alternating regimen may induce diuresis and correct a low sodium concentration rather than lead to hyponatremia.[69] There remains, however, a residuum of moribund hyponatremic edematous patients, unresponsive to all previous therapeutic endeavors, in whom a trial of hypertonic sodium therapy is warranted as a last-ditch step. After all, experimental evidence exists to indicate that hypotonicity (hypo-osmolarity), as well as decreased plasma and extracellular volumes, may be a factor in circulatory failure.[70] Finally, we must recognize that many hyponatremic patients of the *sodium-water disproportion* type urgently require intelligent disregard of this therapeutically inciting biochemical sign. These patients, comfortably adjusted to their state of hypotonic sin, should be left unmolested by the sodium ion. At the most, they may be bolstered with potassium (if hypokalemia is present) while major therapy is directed toward the underlying disease.

Hyponatremia is a biochemical sign of a series of complex disturbances of the body fluids. At best, these disturbances are still incompletely understood and present a challenge to the physician to exercise his physiologic knowledge, his clinical astuteness, and his therapeutic ingenuity.

J. RUSSELL ELKINTON

REFERENCES

[1] WELT, L. G.: Edema and hyponatremia. Arch. Int. Med. **89:** 931, 1952.

[2] LEITER, L., WESTON, R. E., AND GROSSMAN, J.: The low sodium syndrome: Its origins and varieties. Bull. New York Acad. Med. **29:** 833, 1953.

[3] STEELE, J. M.: Electrolyte disturbances and low salt syndrome. New York J. Med. **53:** 1766, 1953.

[4] MOORE, F. D.: The low sodium syndromes of surgery. J. A. M. A. **154:** 379, 1954.

[5] WYNN, V., AND ROB, C. G.: Water intoxication. Differential diagnosis of the hypotonic syndromes. Lancet **1:** 587, 1954.

[6] NEWMAN, E. V.: Hyponatremic syndrome. Arch. Int. Med. **95:** 374, 1955.

[7] MERRILL, J. P.: The low salt syndromes. Mod. Concepts Cardiovasc. Dis. **24:** 283, 1955.

[8] DANOWSKI, T. S., FERGUS, E. B., AND MATEER, F. M.: The low salt syndromes. Ann. Int. Med. **43:** 643, 1955.

[9] BINGER, M. W., AND KEITH, N. M.: The effect of diuretics in different types of edema. J. A. M. A. **101:** 2009, 1933.

[10] POLL, D., AND STERN, J. E.: Untoward effects of diuresis with special reference to mercurial diuretics. Arch. Int. Med. **58:** 1087, 1936.

[11] KLINGHOFFER, K. A.: Dehydration from diuretics. New Internat. Clinics **1:** 221, 1941.

[12] PETERS, J. P.: The role of sodium in the production of edema. New England J. Med. **239:** 353, 1948.

[13] MACGUIRE, W. B., JR.: Risk of uremia due to sodium depletion. J. A. M. A. **137:** 1377, 1948.

[14] SOLOFF, L. A., AND ZATUCHNI, J.: Syndrome of salt depletion. J. A. M. A. **139:** 1136, 1949.

[15] SCHROEDER, H. A.: Renal failure associated with low extracellular sodium chloride; low salt syndrome. J. A. M. A. **141:** 117, 1949.

[16] JAFFÉ, H. L., MASTER, A. M., AND DORRANCE, W.: The salt depletion syndrome following mercurial diuresis in elderly persons. Am. J. M. Sc. **220:** 60, 1950.

[17] CITRON, D., BERCU, B., LEMMER, R., AND MASSIE, E.: Congestive heart failure and hyponatremia: Untoward effects of mercurial diuresis. Ann. Int. Med. **34:** 872, 1951.

[18] BLACK, A. B., AND LITCHFIELD, J. A.: Uraemia complicating low salt treatment of heart failure. Quart. J. Med. **20:** 149, 1951.

[19] ELKINTON, J. R., SQUIRES, R. D., AND BLUEMLE, L. W., JR.: The distribution of body fluids in congestive heart failure. IV. Exchanges in patients, refractory to mercurial diuretics, treated with sodium and potassium. Circulation **5:** 58, 1952.

[20] MCLESTER, J. S., AND HOLLEY, H. L.: Salt depletion syndrome with increasing edema occurring during mercurial diuretic therapy. Ann. Int. Med. **36:** 562, 1952.

[21] WESTON, R. E., ESCHER, D. J. W., GROSSMAN, J., AND LEITER, L.: Mechanisms contributing to unresponsiveness to mercurial diuretics in congestive failure. J. Clin. Invest. **31:** 901, 1952.

[22] URICCHIO, J. F., AND CALENDA, D. G.: The failure of hypertonic saline in the treatment of hyponatremia and edema in congestive heart failure. Ann. Int. Med. **39:** 1288, 1953.

[23] FARBER, S. J., AND SOBERMAN, R. J.: The relative amounts of body sodium and water in patients with heart, renal or hepatic disease. J. Clin. Invest. **32:** 566, 1953.

[24] MOORE, F. D., EDELMAN, I. S., OLNEY, J. M., JAMES, A. H., BROOKS, L., AND WILSON, G. M.: Body sodium and potassium. III. Inter-related trends in alimentary, renal and cardiovascular disease; lack of correlation between body stores and plasma concentration. Metabolism **3:** 334, 1954.

[25] TALSO, P. J., SPAFFORD, N., FERENZI, G., AND JACKSON, H. O.: Paradoxical hyponatremia associated with congestive heart failure and with cirrhosis of the liver. Metabolism **5:** 58, 1956.

[26] DARROW, D. C., AND YANNET, H.: The changes in the distribution of body water accompanying increase and decrease in extracellular electrolyte. J. Clin. Invest. **14:** 266, 1935.

[27] MCCANCE, R. A., AND WIDDOWSON, E. M.: The secretion of urine in man during experimental salt deficiency. J. Physiol. **91:** 222, 1937.

[28] ELKINTON, J. R., DANOWSKI, T. S., AND WINKLER, A. W.: Hemodynamic changes in salt depletion and in dehydration. J. Clin. Invest. **25:** 120, 1946.

[29] WEIR, J. F., LARSON, E. E., AND ROWNTREE, L. G.: Studies in diabetes insipidus; water balance and water intoxication. Arch. Int. Med. **29:** 306, 1922.

[30] BASKIN, J. L., KEITH, H. M., AND SCRIBNER, B. H.: Water metabolism in water intoxication; review of basic concepts. Am. J. Dis. Child. **83:** 618, 1952.

[31] SWAN, R. C., AND MERRILL, J. P.: The clinical course of acute renal failure. Medicine **32:** 215, 1953.

[32] PETERS, J. P.: Water balance in health and in disease. *In* Diseases of Metabolism, edited by G. G. Duncan, Ed. 3, Philadelphia, W. B. Saunders Co., 1953.

[33] LEQUESNE, L. P., AND LEWIS, A. A. G.: Postoperative water and sodium retention. Lancet **1:** 153, 1953.

[34] ARIEL, I. M.: Effects of a water load administered to patients during the immediate postoperative period. The hypotonic syndrome. Arch. Surg. **62:** 303, 1951.

[35] Elkinton, J. R., and Squires, R. D.: The distribution of body fluids in congestive heart failure. I. Theoretic considerations. Circulation **4:** 679, 1951.

[36] Leaf, A., and Mamby, A. R.: An antidiuretic mechanism not regulated by extracellular fluid tonicity. J. Clin. Invest. **31:** 60, 1952.

[37] Manenson, I. B., Goluboff, B., Grossman, J., Weston, R. E., and Leiter, L.: Studies on water excretion following intravenous hydration and the administration of pitressin or nicotine in congestive heart failure. Circulation **13:** 242, 1956.

[38] Murdaugh, H. V., Jr.: Production of diuresis in hyponatremic edematous states with alcohol. J. Clin. Invest. **35:** 726, 1956.

[39] Lamdin, E., Kleeman, C. R., Rubini, M., and Epstein, F. H.: Studies on alcohol diuresis. III. The response to ethyl alcohol in certain disease states characterized by impaired water tolerance. J. Clin. Invest. **35:** 386, 1956.

[40] Parrish, A. E.: The bioassay of adrenal corticoids in the urine of patients with congestive heart failure. J. Clin. Invest. **28:** 45, 1949.

[41] Singer, B., and Wener, J.: Excretion of sodium-retaining substances in patients with congestive heart failure. Am. Heart J. **45:** 795, 1953.

[42] Hamilton, W. F., Ellison, R. G., Pickering, R. W., Hague, E. E., and Rucker, J. T.: Hemodynamic and endocrine responses to experimental mitral stenosis. Am. J. Physiol. **176:** 445, 1954.

[43] Bartter, F. C., Liddle, G. W., Duncan, L. E., and Delea, C.: The role of extracellular fluid volume in the control of aldosterone secretion in man. J. Clin. Invest. **35:** 688, 1956.

[44] Muller, A. F., Riondel, A. M., Manning, E. L., and Mach, R. S.: Regulation of the secretion of aldosterone in man. J. Clin. Invest. **35:** 725, 1956.

[45] Heidorn, G. H., and Schemm, F. R.: The clinical use of corticotropin (ACTH) and adrenal corticosteroids in the therapy of intractable edema. Am. J. M. Sc. **229:** 621, 1955.

[46] Wolf, A. V.: The Urinary Function of the Kidney. New York, Grune and Stratton, Inc., 1950.

[47] Black, D. A. K.: Renal factors in volume control. The Kidney, CIBA Foundation Symposium. Boston, Little, Brown and Co., 1954, pp. 309.

[48] Elkinton, J. R., and Danowski, T. S.: The Body Fluids; Basic Physiology and Practical Therapeutics. Baltimore, Williams and Wilkins Co., 1955.

[49] Aragh, J. H.: The effect of potassium chloride on hyponatremia. J. Clin. Invest. **33:** 807, 1954.

[50] Cort, J. H., and Matthews, H. L.: Potassium deficiency in congestive heart-failure. Three cases with hyponatremia, including results of potassium replacement in one case. Lancet **1:** 1202, 1954.

[51] Winkler, A. W., and Crankshaw, O. F.: Chloride depletion in conditions other than Addison's Disease. J. Clin. Invest. **17:** 1, 1938.

[52] Westwater, J. O., Stiven, D., and Garry, R. C.: Note on serum sodium level in patients suffering from tuberculosis. Clin. Sc. **4:** 73, 1939.

[53] Sims, E. A. H., Welt, L. G., Orloff, J., and Needham, J. W.: Asymptomatic hyponatremia in pulmonary tuberculosis. J. Clin. Invest. **29:** 1545, 1950.

[54] Rapoport, S., West, C. D., and Brodsky, W. A.: Salt losing conditions; The renal defect in tuberculous meningitis. J. Lab. & Clin. Med. **37:** 550, 1951.

[55] Harrison, H. E., Finberg, L., and Fleishman, E.: Disturbances of ionic equilibrium of intracellular and extracellular electrolytes in patients with tuberculous meningitis. J. Clin. Invest. **31:** 300, 1952.

[56] Welt, L. G., Seldin, D. W., Nelson, W. P., III, German, W. J., and Peters, J. P.: Role of the central nervous system in metabolism of electrolytes and water. Arch. Int. Med. **90:** 355, 1952.

[57] Cort, J. H.: Cerebral salt wasting. Lancet **1:** 752, 1954.

[58] Waterhouse, C., Keutmann, E. H., and Fenninger, L. D.: Studies of electrolyte metabolism in 2 patients with pituitary insufficiency. J. Clin. Endocrinol. **12:** 798, 1952.

[59] Elkinton, J. R., and Huth, E. J.: Hypokalemic alkalosis in anorexia nervosa. Vomiting, starvation, and potassium depletion as etiologic factors. In preparation.

[60] Srikantia, S. G., Venkatachalam, P. S., and Gopalan, C.: Electrolyte studies in nutritional edema. Metabolism **2:** 521, 1953.

[61] Nelson, W. P., III, Rosenbaum, J. D., and Strauss, M. B.: Hyponatremia in hepatic cirrhosis following paracentesis. J. Clin. Invest. **30:** 738, 1951.

[62] Holley, H. L., and McLester, J. S.: Salt depletion syndrome associated with decompensated cirrhosis of the liver. J. A. M. A. **145:** 392, 1951.

[63] Kelly, J. J., Jr., and Deming, Q. B.: Low sodium syndrome and hyperpotassemia induced in edematous patients by mechanical removal of body fluid. Am. J. Med. **10:** 766, 1951.

[64] Wilson, G. M., Edelman, I. S., Brooks, L., Myrden, J. A., Harken, D. E., and Moore, F. D.: Metabolic changes associated with mitral valvuloplasty. Circulation **9:** 199, 1954.

[65] Bruce, R. A., Merendino, K. A., Dunning, M. F., Scribner, B. H., Donohue, D., Carlsen, E. R., and Cummins, J.: Observations on

hyponatremia following mitral valve surgery. Surg., Gynec. & Obst. **100:** 293, 1955.

[66] GOODYEAR, A. V. N., AND GLENN, W. W. L.: Observations on the hyponatremia following mitral valvulotomy. Circulation **11:** 584, 1955.

[67] SCHWARTZ, W. B., AND WALLACE, W. M.: Electrolyte equilibrium during mercurial diuresis. J. Clin. Invest. **30:** 1089, 1951.

[68] RUBIN, A. L., THOMPSON, H. G., JR., BRAVEMAN, W. S., AND LUCKEY, E. H.: The management of refractory edema in heart failure. Ann. Int. Med. **42:** 358, 1955.

[69] — AND BRAVEMAN, W. S.: Treatment of the low-salt syndrome in congestive heart failure by the controlled use of mercurial diuretics. Circulation **13:** 655, 1956.

[70] ELKINTON, J. R., WINKLER, A. W., AND DANOWSKI, T. S.: The importance of volume and of tonicity of the body fluids in salt depletion shock. J. Clin. Invest. **26:** 1002, 1947.

Medical Eponyms

By ROBERT W. BUCK, M.D.

Laennec's Cirrhosis. In the first volume of the famous "Mediate Auscultation, or a Treatise on the Diagnosis of Affections of the Lungs and Heart, Based Chiefly on this New Method of Examination" (*De l'auscultation médiate ou traité du diagnostic des maladies des poumons et du coeur, fondé principalement sur ce nouveau moyen d'exploration*) Paris, 1819, by René Théophile Hyacinthe Laennec (1781–1826), Physician to the Hôpital Necker, there appears in the autopsy report of Observation xxv, Chronic Pleurisy of the Left Side, with Ascites and Organic Disease of the Liver, on page 368, the following description and note:

"The liver, reduced to a third of its usual volume was found hidden, so to speak, in the region it occupied; its external surface, somewhat mammillated and wrinkled, was yellowish gray in color; on incision, it appeared to be entirely made up of a multitude of small round or ovoid granules varying in size from that of a millet seed to that of a hemp seed. There was no space between these granules, which were easily separated from one another, in which an remaining liver tissue could be distinguished. They were fawn-colored, or yellow russet, tending in places to a greenish hue; the tissue of which they were composed was moist, opaque, and rather flabby to the touch, and in pressing the granules between the fingers, only a few were crushed: the remainder felt like a piece of soft leather.

"(Note: This process is one of a variety of conditions which are heterogeneously included under the name of *schirrus*. I am impelled to designate it by the name *cirrhosis* (kippos tawny) because of its color. Its development in the liver is one of the most common causes of ascites and is peculiar in that the liver tissue is absorbed in proportion to the development of the cirrhoses, and often at last disappears completely as in this subject; and that in every case, a liver which contains cirrhoses loses rather than increases in volume.)"

Chagas' Disease

A Clinical, Epidemiologic, and Pathologic Study

By F. S. Laranja, M.D., E. Dias, M.D., G. Nobrega, M.D., and A. Miranda, M.D.

A study of the most important clinical and pathologic aspects of Chagas' disease has been presented, on the basis of the analysis of 180 cases of acute infection (11 with autopsy), 657 cases of chronic asymptomatic infection, and 683 cases of chronic Chagas' heart disease (21 autopsied cases with *Schizotrypanum cruzi* in myocardium).

CONSIDERABLE advances in the clinical aspects of Chagas' disease have been made in the last decade. In the historical review of our knowledge 3 periods may be recognized.[15] 1. The first period began with the clinical descriptions made by Chagas.[2, 3] He described an acute form[4] and several chronic forms[3, 5] of American trypanosomiasis. He was greatly impressed[6, 7] by the cardiac disturbances exhibited by many persons from the region in which the disease was discovered and claimed that such cardiac disturbances were related to chronic American trypanosomiasis.

2. From 1913 to 1943 acute cases of Chagas' disease were described in 15 American countries. Various authorities doubted an etiologic relationship between *Schizotrypanum cruzi* (*Trypanosoma cruzi*) infection and the chronic forms described by Chagas; only a few cases of chronic Chagas' disease were reported up to 1945. The concept of Chagas' disease as an uncommon acute disease was generally accepted. The true medical and social importance of this endemic infection was not appreciated.

3. Carlos Chagas' original observations on the cardiac disturbances in chronic *S. cruzi* infection have been confirmed and considerably extended[10-18] in the last 10 years. Epidemiologic studies, observations of the clinical manifestations, the description of the electrocardiographic changes, improved laboratory diagnosis, the pathologic studies, and, finally, the production of a chronic type of heart disease similar to the human in dogs experimentally infected with *S. cruzi*—all these studies have provided a firm basis for defining chronic Chagas' heart disease as a distinct clinicoanatomic entity.[17]

Observations have shown the common occurrence in some Brazilian districts of both cardiospasm (megaesophagus) and chronic trypanosomiasis. Patients from such areas with cardiospasm show a particularly high percentage (up to 97 per cent) of positive complement-fixation tests for Chagas' disease and electrocardiographic changes similar to those usually found in chronic Chagas' heart disease.[13, 23] These facts suggest a possible etiologic relationship between Chagas' disease and cardiospasm in those areas. The subject requires further investigation.

Etiology

S. cruzi has a typical trypanosome blood form, characterized by a large, terminal or subterminal blepharoplast. In the tissues the flagellates undergo regressive changes resulting in the formation of leishmaniform organisms that divide by binary fission, thus forming intracellular colonies of parasites. The myocardial fibers seem to be the most important site of multiplication of *S. cruzi*.

In sections from the myocardium the parasite usually assumes the morphology of leishmania bodies (fig. 1*a*), which are round corpuscles measuring 4 by 2 or 3 by 1.5 microns, containing an ovoid nucleus and a rodlike blepharoplast. The fibers occasionally contain flagellate or preflagellate forms (fig. 1*b*) of *S. cruzi*; in this case the morphology of individual microorganisms usually is not clearly seen in

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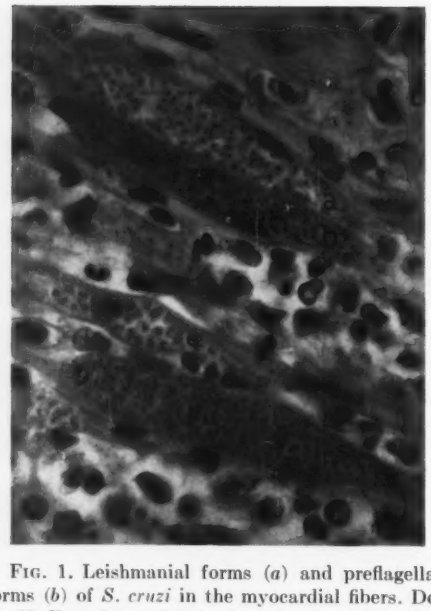


FIG. 1. Leishmanial forms (*a*) and preflagellate forms (*b*) of *S. cruzi* in the myocardial fibers. Dog. no. 35. Experimental infection. Death on the thirty-sixth day of disease, with pronounced cardiac dilatation, right bundle-branch block, atrial fibrillation, and congestive heart failure.

tissue sections. Care should be taken in distinguishing such forms from other intracellular parasites, especially Toxoplasma.

S. cruzi is virulent to man and several animals and is easily cultivated in vitro. Its virulence is variable, depending on the source of the strain and on other factors. The blood trypanosome form is picked up by the insect vector.

EPIDEMIOLOGY, GEOGRAPHIC DISTRIBUTION, AND INCIDENCE

The insect vectors of *S. cruzi* are Hemiptera belonging to the family Reduviidae, subfamily Triatominae. The most important species belong to the genera Triatoma, Panstrongylus, and Rhodnius. More than 30 species of triatomid bugs have been found infected with *S. cruzi*.[8] *Triatoma infestans*, *Panstrongylus megistus*, and *Rhodnius prolixus* are the principal vectors of Chagas' disease in large areas of South and Central America.

Infected triatomid bugs are widely distributed in this continent, from the United States to Argentina (fig. 2). *S. cruzi* has never been detected in triatomes outside the American continent, although it was found in monkeys in Java (Malamos).

FIG. 2. Areas in which triatomid bugs infected with *S. cruzi* have been found. Data collected from the literature up to 1954.

Triatominae are strictly hematophagous insects and they get their flagellates from the blood of vertebrate hosts; so, the presence of infected bugs depends upon the existence of infected vertebrates. To the species well adapted to human dwellings, such as *T. infestans*, *P. megistus*, and *R. prolixus*, man and domestic animals are the main sources of infection.

In rural and semirural areas of the Latin American countries there are huge regions infested with domestic triatomid bugs. The primitive mud huts covered with thatched roofs are favorable habitats for such species. The vectors live in hiding places, in holes and cracks in the walls, in beds, behind trunks, pictures, etc. In the United States there are

several species infected with *S. cruzi*, but they seldom breed in homes, although these are frequently invaded by flying insects during the summertime.

The triatomid bugs harbor *S. cruzi* in their digestive tract and apparently they suffer no harm as a result of being infected with the flagellate. Cyclical development of the parasite takes place in the stomach, duodenum, and rectum of the bugs. The blood trypanosome forms pass through the crithidial (multiplication) stage, and give rise to the metacyclical (infective) forms, which are eliminated with the excreta of the insects. Normally, transmission of the disease is effected through contamination of mucosa or skin with infected dejections eliminated by the bugs during or soon after feeding. Transmission of Chagas' disease to man by blood transfusion, or via placenta, or accidentally by inoculation of blood from infected animals, may occur.

Human infection with *S. cruzi* has been detected so far in all countries over a region extending from the United States (Texas) to Argentina, with the exception of Honduras and British and Dutch Guianas. In the last 10 years a large number of cases of chronic Chagas' heart disease has been diagnosed, particularly in Brazil and Argentina. In some areas of the Brazilian States of Minas Gerais, São Paulo, and Bahia, *S. cruzi* infection is evidently one of the most common etiologic factors of chronic heart disease. Nevertheless, the geographic distribution and incidence of human infection with *S. cruzi* as well as the incidence and severity of chronic Chagas' heart disease in different endemic areas are incompletely known. In most of the huge rural and semirural areas in which infected triatomid bugs have been found, no adequate diagnostic surveys for human cases of Chagas' disease have yet been carried out. There is still a great deal of work to be done, before we shall be able to appreciate the significance of Chagas' disease to the countries of the American Continent.

Acute Chagas' Disease

Acute infection may occur at any age, but usually occurs in the first years of life (fig. 3).

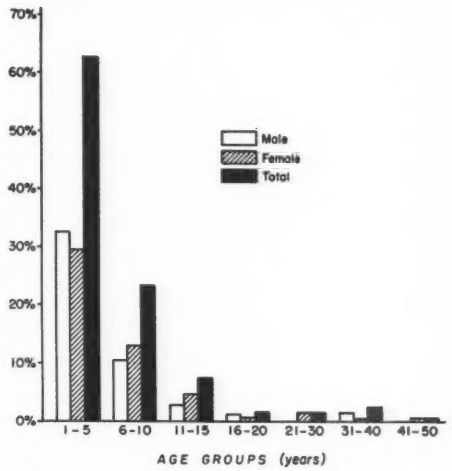


Fig. 3. Age and sex distribution of 171 cases of acute Chagas' disease.

Acute cases are more frequent in the summer months. The clinical picture may be quite easily recognized in endemic areas. The acute period is manifested by general malaise, fever, abundant sweating, muscular pains, irritation, anorexia, and sometimes vomiting and diarrhea; local signs of portal of entry of the parasite in the organism, lymph node enlargement, generalized edema, and in some cases anasarca; hepatomegaly and moderate splenomegaly, and occasionally cutaneous eruptions (schizotrypanides); symptoms and signs of heart involvement, and in some cases (usually fatal) symptoms and signs of central nervous system involvement (acute meningoencephalitis). Laboratory findings include leukocytosis with pronounced lymphocytosis, increased blood sedimentation rate, widening of the coagulation band on Weltman's reaction, decrease in serum albumin fraction, and frequently increase of certain globulin fractions of blood sera during the edematous period, as well as abnormalities of some other liver function tests.

Cardiac Involvement

Cardiac involvement of greater or lesser intensity probably occurs in almost every case of acute Chagas' disease, but is frequently not recognized. A review of the 19 cases of acute Chagas' disease so far reported with post-

TABLE 1.—*Clinicopathologic Findings in Eleven Cases of Acute Chagas' Disease*

Case, reg. no.	Age and sex	Duration of disease (approxim.)	Death	X-ray of chest	Electrocardiogram	Chief anatomic findngs:*	
						Heart	Other organs
1 429 J.S.	2 mos. M	10 days	Bronchopneumonia, pyothorax	Normal cardiac area	Rate: 180; AQRS: approx. +95° AT +35° QT 0.20″	Acute, moderately intense (++), myocarditis, preponderant in subepicardial areas left ventricle; slight degenerative changes of myocardial fibers; edema intima and media of small arteries of right ventricle; numerous myocardial fibers parasited with *S. cruzi*	Bronchopneumonia and fibrinopurulent pleuritis at right side, right pyothorax; fatty degeneration liver
2 519 C.M.S.	5 mos. F	2 mos.	Cardiac failure	—	(Made 7 days before death) Rate: 170 P-R: 0.12″ AQRS: +80° AT +5°	Acute, severe (++++) myocarditis, preponderantly subendocardial and more severe at ventricles; slight degenerative changes of myocardial fibers; *S. cruzi* in myocardial fibers	Passive congestion lungs, liver, and kidneys
3 589 D.S.	7 yrs. F	2 mos.	Cardiac failure, convulsions	—	—	Acute, diffuse myocarditis of slight (+) intensity with disseminated degenerative changes of myocardial fibers; slight degree of fibrosis of left ventricle; *S. cruzi* within myocardial fibers	Passive congestion lungs, liver, and kidneys; fat degeneration of liver
4 588 F.D.	2 yrs. F	3½ mos.	Cachexia	Moderate enlargement of cardiac shadow (pericardial fluid) until 2 weeks before death	Abnormal: Rate: 150. PR 0.16″. Low voltage of QRS in extremity leads. Prolonged Q-T interval. Subendocardial injury pattern	Acute, diffuse, moderately intense (++) myocarditis with slight degenerative changes of myocardial fibers; slight degree of fibrosis of left ventricle; *S. cruzi* within myocardial fibers	Fat degeneration liver and kidneys
5 408 G.M.S.	5 yrs. F	22 days	Convulsions, congestive heart failure	—	Abnormal: Rate: 130. Prolongation of P-R interval. Complete RBBB. Pattern of subendocardial injury, followed by subepicardial injury of anterior wall	Acute, very severe (+++++) diffuse myocarditis, predominantly subendocardial and on the basal portion of the ventricles; severe, disseminated, hyaline degeneration of myocardial fibers; Heavy parasitism of myocardial fibers by *S. cruzi*; Extensive lesions involving all the portions of the His-Tawara system, and apparently more severe in initial portion of right bundle of His	Chagasic encephalitis; tuberculosis bronchial and hilar lymph nodes; serous hepatitis; anasarca (bilateral hydrothorax, hydropericardium, and hydroperitoneum); passive congestion of lungs, spleen, kidneys, and adrenal glands

252 A.S.	yrs. M	mos.	Convulsions	Normal cardiac area (27 days before death)	Abnormal: Rate: 136. QRS 0.07″. AQRS approx. +135°. AT approx. +90°. T wave neg. in V_1, pos. in V_2 and diphasic −+ in V_5, V_6.	Acute, severe (+++) diffuse myocarditis, with moderately severe degenerative changes of myocardial fibers and interstitial fibrosis; lesions were more severe in ventricles, particularly left; circumscribed pericarditis; *S. cruzi* in myocardial fibers	Passive congestion [illegible] liver, kidneys, and spleen
7 295 J.B.	4 yrs. M	6 mos.	Congestive heart failure	—	Abnormal: Rate: 185. Prolongation of P-R interval. Low voltage of QRS and T waves. AQRS +110°. AT +10°.	Acute, diffuse myocarditis of slight (+) intensity, with slight degree of degenerative changes of myocardial fibers and conspicuous interstitial fibrosis of myocardium; circumscribed acute pericarditis; area of fibrous thickening of endocardium at base of left ventricle; *S. cruzi* in myocardium	Edema and hyperemia of lungs; bronchopneumonia; pulmonary infarction; fat degeneration of liver
8 270 J.C.	2 yrs. M	6 mos.	Congestive heart failure	—	Abnormal: Rate: 140. Low voltage QRS extremity and precordial leads. AQRS +90°. Low T waves in standard leads, neg. in V_1, V_2, V_3, diphasic −+ in V_4, isoelectric in V_5	Acute, severe (+++), diffuse and focal myocarditis with slight degree of degenerative changes of myocardial fibers; moderate interstitial fibrosis; various myocardial fibers, particularly in left ventricle, parasited with *S. cruzi*; conspicuous reduction of lumen of anterior descending coronary artery by atheromatous (?) plaque	Passive congestion of lungs, liver, spleen, and kidneys
9 1650 E.L.E.	10 mos. M	20 days	Convulsions	—	Abnormal: Rate: 150. Low voltage of P waves and QRS complex in extremity leads. QRS 0.06″. AQRS approx. −170°. AT approx. +45°. Incomplete RBBB?	Acute, diffuse, moderately severe (+++) myocarditis, with degenerative changes of myocardial fibers; various myocardial fibers with *S. cruzi*. Edema of intima of anterior coronary artery	Chagasic encephalitis; passive congestion of lungs, liver, and spleen; fat degeneration of liver
10 2284 J.T.M.	2 yrs. 6 mos. M	2 mos.	Congestive heart failure	—	Abnormal: Low voltage of QRS in extremity leads; left axis deviation	Acute very severe (+++++), focal and diffuse myocarditis with relatively few *S. cruzi* in myocardial fibers; acute pericarditis over basal portion of left ventricle	Passive congestion of lungs, liver, spleen, and kidneys; fat degeneration of liver; lymphoid hyperplasia of spleen
11 1500 Ub C.S.	15 mos. F	40 days	Congestive heart failure	—	—	Acute, very severe (+++++), diffuse myocarditis with many myocardial fibers parasited with *S. cruzi*; circumscribed acute pericarditis at base of right ventricle	Passive congestion lungs, liver, and spleen; fat degeneration of liver.

* In cases 5 and 6 autopsy was performed by Dr. Torres and Dr. Duarte, Division of Pathology, Instituto Oswaldo Cruz; in the remaining cases only the heart and fragments of some organs were available for microscopic examination.

mortem examination leaves the impression that in most if not in all these cases, the heart lesions were essentially autopsy findings whose full clinical importance would hardly be appreciated during life. An acute, severe, diffuse myocarditis with leishmanial forms of *S. cruzi* in myocardial fibers was present in all the 19 autopsy cases from the literature, and in most of them there were also abundant pericardial transudate and signs of passive congestion in various organs. Specific inflammatory lesions of the central nervous system (acute meningoencephalitis) were also found in several of these 19 cases.

In our own series of 11 autopsy cases of acute Chagas' disease from Bambuí (table 1) the chief anatomic findings were similar to those of the 19 previously reported cases: acute myocarditis (fig. 4) with *S. cruzi* in myocardial fibers in all the 11 cases; anatomic evidences of circulatory failure in 8 cases; chagasic encephalitis in 2 cases (the nervous system was not examined in the remaining cases); pronounced fatty degeneration of the liver in 7 cases.

With the exception of the frequency and severity of the heart lesions, the manifestations of acute Chagas' heart disease do not differ essentially from those due to acute myocarditis of other etiologies.

In severe cases the picture of bilateral heart failure (pulmonary and systemic congestion, bilateral increase of cardiac shadow, regular heart rhythm, accelerated heart rate, gallop

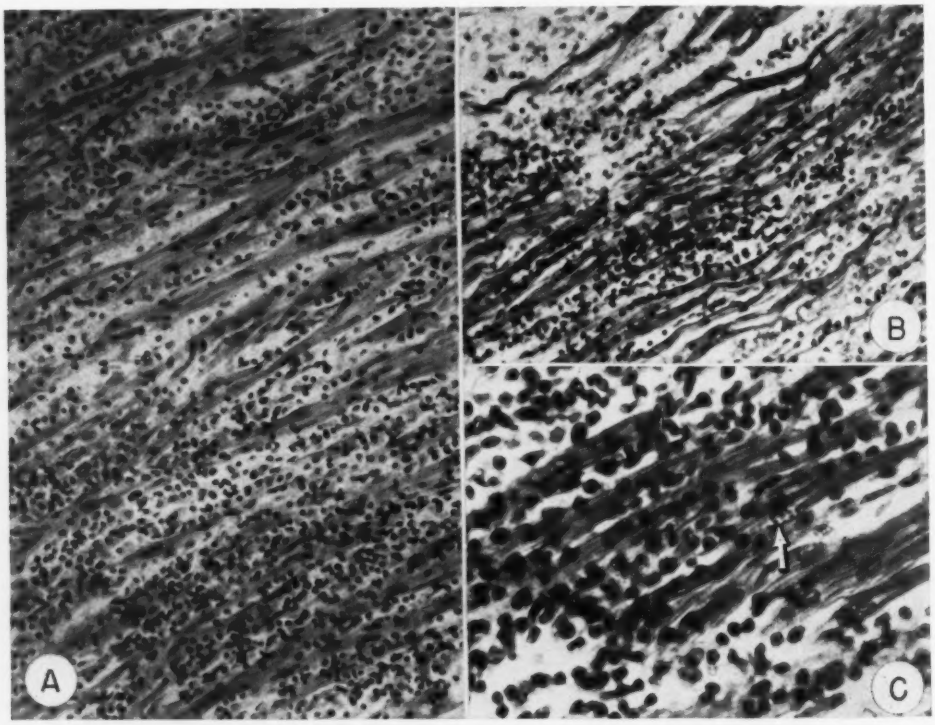


FIG. 4. Acute myocarditis: *A*. Case no. 11 (table 1). Patient aged 15 months. Acute myocarditis of approximately 40 days' duration. The muscle fibers are separated by a diffuse infiltration of mononuclear cells (H & E × 200). *B*. Case no. 8 (table 1). Patient aged 2 years. Myocarditis of approximately 6 months' duration. Diffuse inflammatory infiltration, loss of muscle substance and some degree of proliferation of the interstitial connective tissue (H & E × 220). *C*. Same patient as in *B*. The cellular exudate consists of lymphocytes, monocytoid cells, and histiocytes. One myocardial fiber is seen (arrow) with leishmanial forms of *S. cruzi* (H & E × 440).

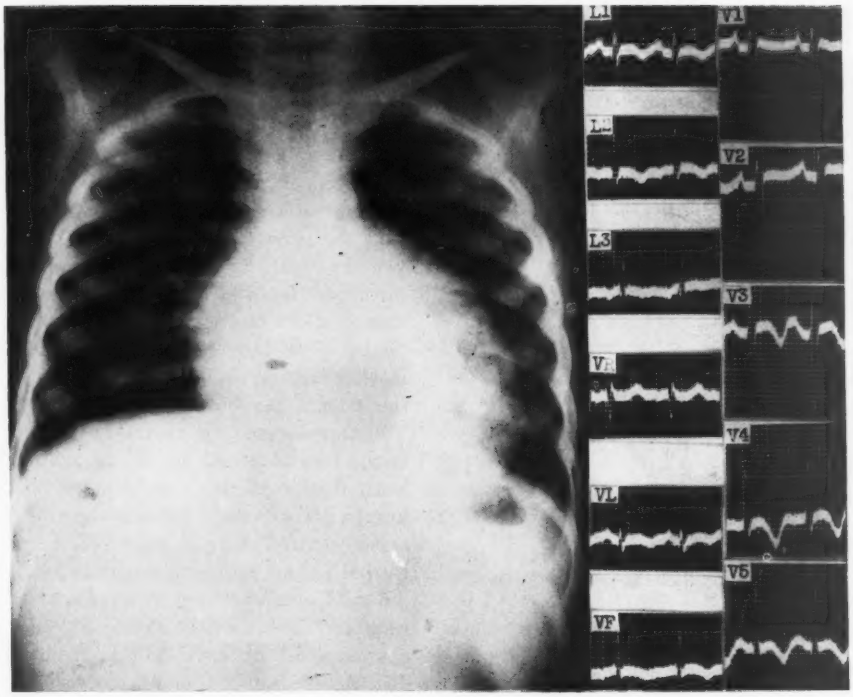


FIG. 5. Acute Chagas' heart disease. Case no. 1833. Marked enlargement of the cardiac shadow, particularly to the left, in the sixth week of infection. Primary T-wave changes. The cardiac shadow and the electrocardiogram reverted to normal at the fourth month of infection.

rhythm or embryocardia (tic-tac rhythm), decreased systolic and low pulse pressure with small radial pulse) allows the clinical diagnosis of myocarditis to be made without difficulty. The convulsive syndrome frequently exhibited by children with severe forms of the disease may be in some cases related to acute circulatory failure.

In mild cases detection of the acute myocarditis by physical examination is less acurate; gallop rhythm with diminution of the intensity of the first heart sound (delayed A-V conduction time) and signs of cardiac dilatation may be the only reliable physical signs of myocardial involvement. Serial x-ray examination of the chest and electrocardiography are the most accurate methods for detecting acute Chagas' heart disease. Enlargement of the cardiac shadow is present in the majority of patients with acute Chagas' disease. It is diffuse and may be moderate or pronounced (fig. 5). The form and the variations in the size of the cardiac shadow suggest that pericardial effusion is often an important factor in the increased cardiac shadow.[13] Usually the cardiac silhouette returns to normal earlier than the electrocardiogram.

Electrocardiographic abnormalities were present in 78 (43.3 per cent) of a group of 180 (159 nonfatal and 21 fatal) patients with acute Chagas' disease. The most common electrocardiographic changes in the entire group of cases of acute Chagas' disease (table 2) were prolongation of P-R interval, primary T-wave changes, low voltage of QRS, prolongation of Q-T interval, and associated ST-T changes ("injury-ischemia pattern").

Comparing the findings in the nonfatal (159 cases) and in the fatal group (21 cases, 11 with postmortem examination) of patients (table 2) the following observations may be made.

TABLE 2.—*Electrocardiographic Changes in 180 Patients (159 Nonfatal and 21 Fatal) with Acute Chagas' Disease*

	Nonfatal: 159 patients		Fatal: 21 patients		Total: 180 patients	
	No. of cases*	%	No. of cases*	%	No. of cases*	%
Abnormal electrocardiogram	60	37.7	18	85.7	78	43.3
Prolongation of P-R	32	20.1	7	33.3	39	21.7
Primary T-wave changes	28	17.6	7	33.3	35	19.4
Prolongation of Q-T interval	12	7.5	1	4.7	13	7.2
ST-T changes (injury-ischemia pattern)	4	2.5	4	19.0	8	4.4
Low voltage of QRS	7	4.4	8	38.1	15	8.3
P-wave abnormalities	4	2.5	1	4.8	5	2.8
Ventricular extrasystoles	3	1.9	1	4.8	4	2.2
Nodal rhythm	1	0.6	—		1	0.5
RBBB, complete			2	9.5	2	1.1

* Two or more types of electrocardiographic changes were frequently present in the same patient.

1. Myocardial damage was detected by the electrocardiogram in a high (85.7 per cent) percentage of cases from the fatal group. In the nonfatal group only 37.7 per cent showed electrocardiographic abnormalities.

2. Prolongation of P-R interval and primary T wave changes were frequent in the nonfatal group, but had a significantly higher (33.3 per cent) incidence in the fatal group.

3. S-T displacements associated with T-wave changes ("injury-ischemia") and low voltage of QRS were uncommon in the nonfatal and had a significantly high incidence in the fatal group.

4. The only 2 cases of intraventricular block (right bundle-branch block) were in the fatal group.

A comparison of tables 2 and 3 calls attention to the marked differences in the type and incidence of electrocardiographic abnormalities in acute and chronic Chagas' heart disease. Also from the clinical and pathologic standpoints, acute and chronic Chagas' heart disease each have quite distinctive features. As a matter of fact, these 2 types of heart disease seem to have in common only the etiologic agent and a widespread inflammatory process of the myocardium.

The diffuse myocardial lesions in acut Chagas' disease tend to alter the ventricula complex and cause only minor degrees of A-V conduction disturbances. They are usually no apt to produce marked conduction disturbance nor to set up frequent ectopic contraction Electrocardiographic-anatomic correlations i our human and experimental material indicat that the spread of excitation to the atria an ventricles is apparently not significantl disturbed despite the severe, diffuse, acut inflammatory myocardial lesions; only whe dilatation of heart cavities or proliferation o interstitial connective tissue takes place d significant conduction disturbances appear. The appearance of intraventricular bloc (right bundle-branch block) in acute Chagas' heart disease carries a poor prognosis; in our human and experimental material this disturbance occurred only in cases of severe myocardial lesions and cardiac dilatation. A quite different prognostic significance is attached to right bundle-branch block in chronic Chagas' heart disease; in this condition the conduction disturbance may be found in cases showing only limited cicatricial inflammatory myocardial lesions without cardiac enlargement, and may be compatible with long survival of the patient.

Diagnosis

Laboratory diagnosis of acute Chagas' disease is based on the demonstration of the parasite. In the first weeks of infection the high level of parasitemia permits demonstration of circulating forms (trypanosomes) of *S. cruzi* in a fresh blood smear or a thick drop preparation of blood. As the infection evolves, the number of blood circulating trypanosomes decreases; after the sixth to tenth weeks of infection direct microscopic demonstration of the parasite in the blood is difficult. At this time, xenodiagnosis,* animal inoculation of blood, or blood culture are the recommended procedures for demonstration of the parasite. A precipitin reaction proposed by Muniz and

* A diagnostic method proposed by Brumpt, consisting in feeding uninfected laboratory-bred triatomid bugs on patients and examining the bugs' feces for the presence of *S. cruzi* 2 to 3 months after feeding.

TABLE 3.—*Electrocardiographic Changes in 683 Patients with Chronic Chagas' Heart Disease (Including 200 Fatal Cases)*

	Non fatal: 483 patients		Fatal: 200 patients		Total: 683 patients	
	No. of cases*	%	No. of cases*	%	No. of cases*	%
Atrial-ventricular block	174	36.0	74	37.0	248	36.3
First degree A-V block	138	28.6	30	15.0	168	24.6
Second degree A-V block	14	2.9	10	5.0	24	3.5
Complete A-V block	22	4.5	34	17.0	56	8.2
right BBB type of QRS	14	2.9	27	13.5	41	6.0
left BBB type of QRS	2	0.4	—		2	0.3
indeterminate BBB type of QRS	3	0.6	1	0.5	4	0.6
right and left BBB type of QRS	1	0.2	6	3.0	7	1.0
normal duration of QRS	2	0.4	—		2	0.3
Intraventricular block	254	52.6	128	64.0	382	55.9
Complete RBBB	226	46.8	104	52.0	330	48.3
type:						
concordant	43	8.9	23	11.5	66	9.7
S-wide	128	26.5	29	14.5	157	23.0
discordant	44	9.1	26	13.0	70	10.2
"atypical"	11	2.3	26	13.0	37	5.4
associated with QRS changes in lead I or left precordial leads						
Slurring of R; delayed intrinsicoid deflection	6	1.2	21	10.5	27	3.9
Signs of left ventricular enlargement	2	0.4	8	4.0	10	1.5
Signs of necrosis of anterior wall	6	1.2	25	12.5	31	4.5
associated with ST or T wave changes	27	5.6	39	19.5	66	9.7
Incomlplete RBBB (nonisolated)	18	3.7	4	2.0	22	3.2
Compete LBBB	6	1.2	9	4.5	15	2.2
Incomplete LBBB	4	0.8	11	5.5	15	2.2
QRS-T changes without intraventricular block						
Signs of left ventricular enlargement	11	2.2	13	6.5	24	3.5
Isolated QRS changes	33	6.8	29	14.5	62	9.1
Primary ST-T changes	62	12.8	26	13.0	88	12.9
Abnormalities of P wave	27	5.6	46	23.0	73	10.7
Premature contractions	166	34.4	161	80.5	327	47.9
Supraventricular	11	2.3	8	4.0	19	2.8
Ventricular	153	31.7	138	69.0	291	42.6
Extrasystolic ventricular tachycardia	2	0.4	15	7.5	17	2.5
Paroxysmal tachycardia	3	0.6	13	6.5	16	2.3
Supraventricular	1	0.2	1	0.5	2	0.3
Ventricular	2	0.4	12	6.0	14	2.0
Atrial fibrillation or flutter	13	2.7	32	16.0	45	6.6
Nodal rhythm. Isorhythmic A-V dissociation	2	0.4	4	2.0	6	0.9

* Two or more types of electrocardiographic changes were frequently present in the same patient.

Freitas[24] has shown consistently positive results in our acute cases. Complement-fixation test (Guerreiro-Machado's reaction) may yield negative results in the early stages of acute infection; it is a valuable procedure for the diagnosis of chronic Chagas' disease.

Mortality

Mortality during the acute period of Chagas' disease in 235 cases from Bambuí reached 9.4 per cent (22 cases). Death is due to congestive heart failure, convulsive seizures, or to associated infection. The acute infection is more severe in early infancy; in adolescents and adults it is rarely fatal.

Chagas' disease has a protracted course. The acute period gradually passes over into the chronic stage of the disease.[13] The acute manifestations subside, but the patient remains infected, possibly for the rest of his life. In endemic areas, patients are subject to repeated reinfections. It is not known whether or not such reinfections play any role in the course of the disease. We know that patients kept away from endemic areas for many years remain infected and that the chronic heart involvement may progress.

In most cases the manifestations of acute Chagas' heart disease disappear in a few months or years.[11-13] Some patients may show residual electrocardiographic abnormalities. From a group of 72 cases of acute Chagas' heart disease, followed from 4 to 10 years (average: 7 years, 5 months) in Bambuí, 11 patients (15.3 per cent) showed electrocardiographic abnormalities (9 with prolongation of P-R). It seems probable that such electrocardiographic changes represent active myocarditis (in 1 patient incomplete right bundle-branch block changed to complete right bundle-branch block) but no anatomic studies are as yet available from this group of cases.

Asymptomatic Period of Chronic Infection

Subsidence of the clinical manifestations and reduction of the number of trypanosomes in the blood to such levels that they can no longer be seen on direct fresh examination are the usual criteria for distinguishing the acute from the chronic stages of the disease.

The asymptomatic period, described[13] as the chronic indeterminate form of the disease, comprises a long period, usually from 10 to 20 years, between the end of the acute stage and the establishment of the late heart disease of chronic infection. Patients during the asymptomatic period may be considered as belonging to the category of potential cardiac disease.

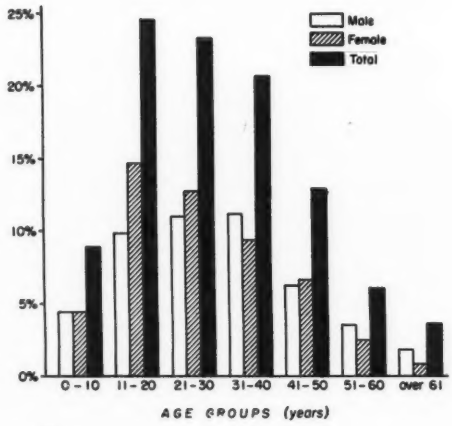
In the first years following the acute infection, these patients show some degree of enlargement of the superficial lymph nodes, occasionally moderate enlargement of the liver, as well as periods of slight, irregular elevations of temperature, increased blood sedimentation rate, and moderate lymphocytosis. In other cases the infection seems to remain mostly inactive for long periods of time.

Transition from the asymptomatic phase to the stages of heart disease in chronic infection is sometimes difficult to define clearly, since many patients develop transient electrocardiographic changes long before the appearance of the permanent cardiac manifestations of chronic Chagas' heart disease. From a group of 75 patients with a known acute period of infection (40 with normal electrocardiogram), 17 (22.7 per cent) developed electrocardiographic abnormalities during an average observation period of 10 years after the acute infection; the electrocardiographic changes were transient in 5 and permanent in 12.

In the endemic areas this group of asymptomatic chronic infection is the largest of the 3 groups of patients with *S. cruzi* infection. Although these patients are apparently healthy and asymptomatic, they are most important from the epidemiologic standpoint.

Age and Sex

There was no significant variation in the incidence of chronic infection according to sex in the entire group of 1,340 patients (males 650, females 690). Two thirds of the cases were between 11 and 40 years of age; 83.5 per cent were between 11 and 50 years (fig. 6). A significant preponderance of females (60.1 per cent) was observed in a group of 657 patients (females 390, males 267) (fig. 7) in the chronic asymptomatic stage of infection. In this group 83.6 per cent of the patients were in the



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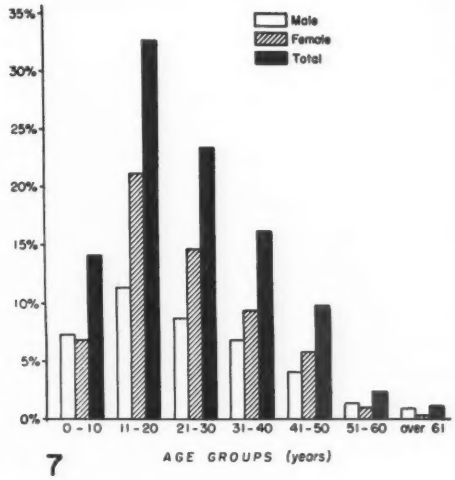

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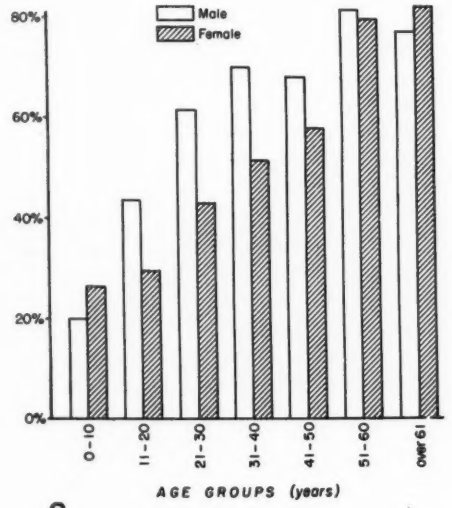

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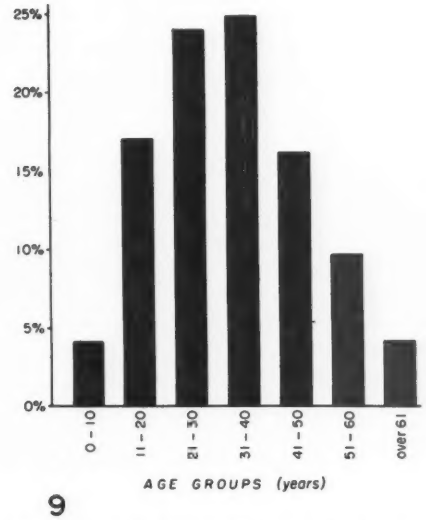

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FIG. 6. Age and sex distribution of 1,340 cases of chronic *S. cruzi* infection (683 with heart involvement and 657 without evidences of heart disease).

FIG. 7. Age and sex distribution of 657 cases of chronic *S. cruzi* infection without evidences of heart involvement.

FIG. 8. Incidence of heart involvement according to sex in different age groups of 1,340 patients with chronic *S. cruzi* infection.

FIG. 9. Age distribution of 683 cases of chronic Chagas' heart disease.

a e groups from 11 to 50 years, the highest n mber of cases (51.2 per cent) being between 1 and 30 years of age.

CHRONIC CHAGAS' HEART DISEASE

From a medical point of view it may be s ted that a clinical diagnosis of chronic *S. cruzi* infection in man rests on the recognition of chronic Chagas' heart disease.

Incidence

During the period 1943–1955, approximately 2,100 chronic and 280 acute cases of Chagas' disease were diagnosed in Bambuí, Minas

Gerais. From the group of 1,340 chronic cases in which electrocardiograms were recorded, 683 (50.9 per cent) patients showed evidences of myocardial damage. Since 1945, when we reported[10] our first cases, up to the present time approximately one half of the patients with chronic *S. cruzi* infection showed evidence of heart damage. The sample is not an unselected one, for many cardiac patients seek medical care in our Department. A survey made[18] in the unselected population from 5 to 60 years of age in the same endemic area disclosed an incidence of 32.7 per cent of chronic heart damage in the group with chronic *S. cruzi* infection. Many cases of severe chronic Chagas' heart disease have been reported recently by various authors from the States of Minas Gerais, São Paulo, Bahia, Goiás, and Pernambuco, as well as from Argentina, Venezuela, and Educador. Variations seem to occur in the incidence and severity of myocardial damage in chronically infected patients from different endemic areas.[13-15]

Age and Sex

A progressive increase in incidence of heart involvement in different age groups of 1,340 patients with chronic *S. cruzi* infection was observed (fig. 8).

In this same group of patients, heart damage showed variations in its incidence according to sex in the different age groups (fig. 8): the males were preponderant in the age groups 11 to 50 and the females were slightly preponderant in the age groups up to 10 and over 61 years of age.

In the group of 683 cardiac patients, 383 (56 per cent) were males and 300 (44 per cent) were females.

Figure 9 shows that 82 per cent of the patients with chronic Chagas' heart disease are in the age groups from 11 to 50 years and that two thirds of these cases are between 11 and 40 years of age. There are a few cases under 10 and over 50 years of age.

From figures 3, 7, and 9 it will be observed that acute infection occurs in the first decade, the chronic asymptomatic cases are preponderant in the second and third decades, and that chronic Chagas' heart disease has its highest incidence in the third and fourth decades of life.

Symptoms and Signs

The manifestations of chronic Chagas heart disease depend mainly on the severity of the myocardial lesions, on the presence of heart failure, and on the type of arrhythmia.

In the early stages of chronic myocardial damage the patient may have no symptoms and the cardiac shadow may be normal or only slightly enlarged. In such patients, who are usually in the first or second decades of life, the diagnosis of the heart disease rests mainly on the electrocardiographic abnormalities.[10] Even severe heart disease, manifested by cardiac enlargement and advanced degrees of A-V or intraventricular block or other electrocardiographic abnormalities, may be unaccompanied by symptoms. One is impressed in some cases by the scarcity of subjective manifestations in contrast with the severity of the objective signs of advanced heart disease.

Cardiac failure usually assumes the type of right and left ventricular failure, with pronounced systemic congestion. A predominantly right-sided type of heart failure with functional tricuspid regurgitation is frequently observed in patients with advanced congestive failure. Isolated left ventricular failure may be present, however, in the early stages of heart failure.

Physical examination shows irregularities of cardiac rhythm usually due to ventricular premature contractions or A-V block, signs of enlargement of the heart (due mainly to dilatation), and evidences of passive congestion (usually more pronounced in the systemic circulation).

Reduplication of the second pulmonic sound is commonly heard. Gallop rhythm, a muffled first heart sound at the mitral area, and systolic murmurs due to functional mitral or tricuspid regurgitation may be present in patients with congestive heart failure. Marked increase of systemic venous pressure and pronounced enlargement of the liver with occasional pulsation are usual findings in these patients. Systolic blood pressure is normal or more commonly, moderately lowered, and the

pulse pressure is usually reduced; the radial pulse is small and irregular.

Roentgenography

X-ray pictures of the chest show moderate to pronounced, diffuse enlargement of the cardiac shadow and evidences of passive congestion in the lungs. Pulmonary congestion in many cases is not marked. Clear pulmonary fields together with marked bilateral enlargement of the heart shadow (fig. 10) is a common finding in the chest x-ray of patients with advanced chronic Chagas' heart disease.

Electrocardiography

Recent advances in the knowledge of Chagas' heart disease are due mostly to the electrocardiographic studies during the last decade. The diagnostic value and several peculiar features of the electrocardiographic findings in chronic Chagas' heart disease have been established[10, 12, 13] on the basis of analysis of data from comparatively large groups of patients. These findings have been extensively confirmed by various authors in studies of cases from different endemic areas.

The electrocardiographic abnormalities in a group of 683 patients with chronic Chagas' heart disease (table 3), from Bambuí, are similar to our previous findings. A great variety of electrocardiographic abnormalities are observed. Complete right bundle-branch block, partial and complete A-V block, ventricular premature contractions, QRS abnormalities or primary T-wave changes, and abnormalities of P waves were common findings. Two or more of these abnormalities were found in the same patient in approximately one third of the cases. On the other hand, ectopic atrial rhythms or contractions, complete left bundle-branch block, high voltage of QRS with or without secondary ST-T changes, and marked ST displacements (injury) were unusual findings. Only a small percentage of cases of advanced chronic Chagas' heart disease failed to show conduction disturbances or ventricular premature contractions.

A-V Block. A-V block was present in 36.3 per cent of the cases. Mild A-V block was more common (28.6 per cent) in the nonfatal than

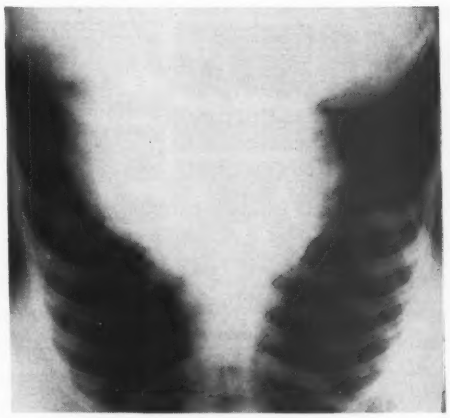

FIG. 10. Case no. 2 (table 4). Patient aged 15. Marked, bilateral enlargement of cardiac shadow in chronic Chagas' heart disease. Clear pulmonary fields.

in the fatal (15.0 per cent) group of cases. First degree A-V block occurs chiefly in the early stages of chronic Chagas' heart diesease,[13] being observed preponderantly in the younger age groups: 72.4 per cent of the cases from the nonfatal group were under 30 years of age. It was the most common (55.2 per cent of the cases) electrocardiographic abnormality present in the age group 11 to 20 years in the 483 nonfatal cases. Intravenous administration of 1 mg. of atropine sulfate may temporarily restore the A-V conduction time to normal; ocular compression may increase the degree of A-V block, with appearance of dropped ventricular beats in patients in the younger age groups.

Chronic *S. cruzi* infection was by far the most common cause of advanced A-V block in patients under 50 years of age in the endemic area that we studied. A comparatively high incidence of advanced A-V block was observed in chronic Chagas' heart disease[10]: second degree A-V block occurred in 3.5 per cent and complete A-V block in 8.2 per cent of the cases from the entire group of 683 patients with chronic Chagas' heart disease. A particularly high incidence (17 per cent) of complete A-V block was found in the group of 200 fatal cases. Ninety per cent of the cases of complete A-V block from this group were 21 to 50 years of

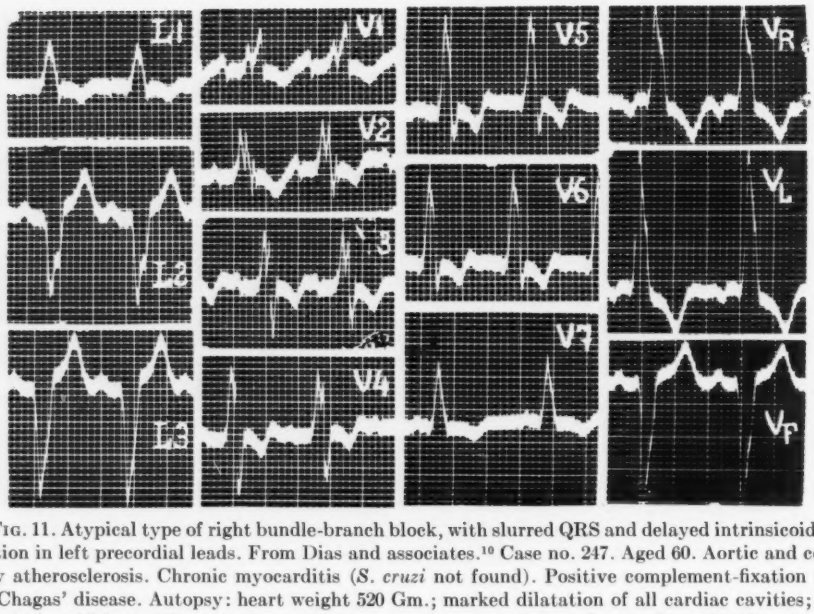

FIG. 11. Atypical type of right bundle-branch block, with slurred QRS and delayed intrinsicoid deflection in left precordial leads. From Dias and associates.[10] Case no. 247. Aged 60. Aortic and coronary atherosclerosis. Chronic myocarditis (*S. cruzi* not found). Positive complement-fixation test for Chagas' disease. Autopsy: heart weight 520 Gm.; marked dilatation of all cardiac cavities; left ventricular thickness 12 mm. at base and 1 mm. at apex; mural thrombus, endocardial fibrosis, and pseudoaneurysm at the apex of left ventricle; diffuse mononuclear infiltration and fibrosis of myocardium, more severe in the left ventricle.

age. Normal duration of QRS is unusual in cases of complete A-V block; most cases have a widened and slurred QRS of the right bundle-branch block type, sometimes with high voltage.

Right Bundle-Branch Block. This is the most frequent conduction disturbance in chronic Chagas' heart disease.[10, 12] The high incidence of right bundle-branch block contrasts with the rarity (2.2 per cent) of complete left bundle-branch block. The presence of complete right bundle-branch block in patients under 50 years of age from endemic areas has a high diagnostic value.[13] In the endemic area that we studied, Chagas' disease was by far the most common cause of right bundle-branch block. In the nonfatal group right bundle-branch block was found in patients from 6 to 65 years of age, but 88 per cent of the cases were in the age groups 11 to 50 years. The incidence was only slightly higher in the fatal (52.0 per cent) than in the nonfatal (46.8 per cent) group of cases. However, some types of right bundle-branch block had a markedly different incidence in the 2 groups of cases: the wide S type (types 2 and 3) was more common in the nonfatal (26.5 per cent) than in the fatal (14.5 per cent) group, while concordant (type 1) and discordant (types 4 and 5) types were slightly, and the *atypical* type of right bundle-branch block (fig. 11) distinctly more frequent in the fatal than in the nonfatal group of cases. The Rs or qR type of QRS in lead I in the *atypical* type of right bundle-branch block may be changed to a qRS type when the record is made with the patient lying on his right side. Association of right bundle-branch block with conspicuous slurring of R deflection and delayed intrinsicoid deflection, or with a qR type of QRS and high R waves in left precordial leads, was more common in the fatal group of cases. These QRS changes are mostly found in patients over 40 and may in some cases be related to predominant left ventricular enlargement and fibrosis (cases 20, 21, table 4). QRS changes suggesting an anterior wall area of myocardial necrosis (usually in leads V_3, V_4, V_5) was a fairly frequent finding in the fatal group (fig. 12). Three patients with such QRS changes had an area of thinning of the cardiac wall a

the apex of left ventricle (cases no. 15, 17, 18), but in 3 other cases with similar electrocardiographic changes myocardial thinning was not found (cases no. 5, 10, 19, table 4). The typical pattern of myocardial infarction may occasionally be found (fig. 13). On a basis of morphologic analysis of the electrocardiogram, primary abnormalities of the final phase of the ventricular complex was diagnosed in 5.6 per cent of cases in the nonfatal and in 19.5 per cent of cases of the fatal group. It was not possible to exclude digitalis effect in several such cases.

QRST Changes without Intraventricular Block. This group includes chiefly patients of the more advanced age groups in whom no adequate electrocardiographic studies were made. Absence of intraventricular block was found in 44 patients (22 per cent) out of the 200 fatal cases; 11 such cases presented A-V block, without intraventricular block; the remaining 33 patients showed no type of heart block. If the cases in which more than 1 year elapsed between the last electrocardiogram and death of the patient are excluded, only 12 cases (6 per cent) remain in the group without heart block. Nevertheless it may be concluded that the absence of conduction disturbances in fatal cases of chronic Chagas' heart disease is quite uncommon.

Premature Ventricular Contractions. These are common in chronic Chagas' heart disease and were observed in 69.0 per cent of the patients in the fatal group. They are frequently bigeminal, independent of digitalis effect, and commonly multiple and polytopic and increased in number by effort. Runs of ventricular extrasystoles forming bouts of extrasystolic ventricular tachycardia (fig. 14) are seen in patients with advanced heart disease, particularly when under digitalis therapy. More prolonged attacks of ventricular paroxysmal tachycardia may appear spontaneously or under the influence of effort. Patients showing polytopic ventricular premature contractions are prone to sudden death. Digitalis should be employed cautiously.

Abnormalities of P Waves, Atrial Fibrillation or Flutter. A high incidence of marked abnormalities of P waves (23 per cent) and of atrial fibrillation or flutter (16 per cent) was observed in the fatal group of cases, in contrast with the low incidence of these changes in the nonfatal group. The severe prognostic significance of atrial fibrillation in chronic Chagas' heart disease was pointed out by Chagas.[5, 7] Its incidence is higher in the older age groups, but its severity is greater in young patients.

In the autopsy series (table 4) there were 8 patients with marked abnormalities of P waves and 6 patients with atrial fibrillation or flutter. No correlation was found between these electrocardiographic changes and the presence of atrial thrombosis or pulmonary infarcts. Cardiac enlargement was present in all the cases but varied greatly. Congestive heart failure was present in all cases.

Diagnosis

Consideration of the possibility of Chagas' disease in young or middle-aged patients who have been infected with *S. cruzi* in endemic areas of the disease and who present a chronic nonvalvular type of heart disease is the first prerequisite for a correct etiologic diagnosis.

The clinical history is of utmost importance. Detailed information should be obtained on epidemiologic factors operating in the area where the patient was born or has lived (existence of the insect vectors, the type of house the patient has inhabited, the presence of bugs in the house, etc.). A history of heart disease with congestive failure or sudden death in other members of the same family or in other young individuals from the same region is commonly elicited. Patients with the chronic type of heart disease rarely give a clear history of the initial stage of the infection, for this usually occurs in the first years of life. A complement-fixation test for Chagas' disease should be made in any young or middle-aged patient from endemic areas of the disease presenting a myocardial type of heart disease, with conduction disturbances, ventricular premature contractions, diffuse enlargement of the heart, with or without manifestations of congestive heart failure. Complete right bundle-branch block and complete A-V block (usually associated with ventricular premature contractions) in patients under 50 years, from endemic

TABLE 4.—*Clinicopathologic Findings in Twenty-One Cases of Chronic Chagas' Heart Disease with* S. Cruzi *in Myocardial Fibers*

Case, reg. no.	Age (years) and sex	Clinical findings	Anatomic findings*
1 222	6 F	CHF 25 days; acute infection probably occurred 3 years ago; Enlarged superficial lymph nodes; sinus tachycardia; AQRS +60°; low voltage slurred QRS standard leads; prolonged Q-T interval; AT −60°; isoelectric T in V_4, V_5	Chronic, diffuse and focal myocarditis, extensive areas fibrosis, preponderantly subendocardial; endocardial thickening base of left ventricle; CPC lungs, liver, spleen, and kidneys; fat degeneration liver
2† 1.847	15 M	CHF 1 year; marked, bilateral cardiac enlargement. ECG: atrial fibrillation and flutter, complete A-V block, multiple, polytopic ventricular extrasystoles, paroxysmal ventricular tachycardia	HW: 665 Gm.; H & D; aneurysm apex of left ventricle; chronic, diffuse and focal myocarditis; circumscribed pericarditis base left ventricle; moderate intimal hyperplasia small and medium-sized branches coronary arteries; CPC lungs, liver, spleen, and kidneys
3† 160	22 M	CHF 5 years; Adams-Stokes seizures; marked, bilateral cardiac enlargement; ECG; complete A-V block	HW 720 Gm.; H & D, marked; thrombosis right atrial appendage; endocardial fibrosis base left ventricle; chronic myocarditis, ventricles; infarct base of right lung; CPC lungs, liver, spleen, kidneys; medial hypertrophy small intramyocardial arteries; intimal proliferation and edema media of medium-sized coronary arteries
4 193	20 F	CHF 6 months. Functional mitral and tricuspid regurgitation; probable thyrotoxicosis; marked, bilateral enlargement heart. ECG: polytopic, multiple ventricular extrasystoles, runs of paroxysmal ventricular tachycardia, low voltage QRS in standard leads, negative T in L_2, L_3, V_5, V_6, notched R deflections in V_5, V_6	HW 400 Gm.; H & D; mural thrombus and small area thinning apex left ventricle; severe, diffuse, chronic and subacute myocarditis; granulomatous formations with multinucleated giant cells in ventricular myocardium; circumscribed pericarditis base left ventricle; areas infiltrative endocarditis; CPC lungs, liver, spleen, kidneys
5† 1.780	21 M	CHF 8 months; marked, bilateral enlargement cardiac shadow; sudden death; ECG: frequent, polytopic ventricular extrasystoles; prolonged P-R.; type IV RBBB; small R in V_2, V_4	HW 510 Gm.; H & D; chronic myocarditis, with granulomatous formations in right atrium and ventricle; CPC lungs, liver, spleen, kidneys; anasarca; left pulmonary (base) and splenic infarcts; pulmonary tuberculosis; tuberculous lymphadenitis at hilum; miliary tuberculosis spleen
6 1.918	26 M	CHF 7 months; precordial pain on effort; moderate bilateral enlargement of cardiac shadow; ECG: widened notched P waves, multiple, polytopic ventricular extrasystoles, low, slurred QRS in standard leads, AQRS −75°, slurred R in V_5, V_6, QRS-T changes suggesting anterolateral infarction, QS in L_2, L_3, V_F (posterior necrosis?); cardiospasm	HW 390 Gm.; H & D; moderate; extensive mural thrombosis apex left ventricle with marked, local endocardial fibrosis; chronic and subacute diffuse myocarditis, preponderantly left ventricle; epicarditis base left ventricle; fat degeneration liver; CPC lungs, liver, spleen, kidneys
7† J.D.M.	26 M	CHF 8 months; repeated pulmonary embolism; marked, bilateral enlargement heart; ECG: sinus tachycardia, rate 150, polytopic ventricular extrasystoles, incomplete left bundle-branch block	HW 600 Gm.; H & D; thrombosis apex left ventricle and right atrial appendage; chronic, diffuse myocarditis, more severe left ventricle; multiple, bilateral pulmonary infarcts; CPC lungs, liver spleen, kidneys; anasarca
8† 180	28 M	Several bouts CHF last 6 years; Adams-Stokes seizures; marked, bilateral enlargement of cardiac shadow; ECG: complete A-V, block, multiple, polytopic ventricular extrasystoles, atrial fibrillation	HW 750 Gm.; marked H & D; aneurysm apex left ventricle; mural thrombus apex left ventricle; in right atrium and small thrombus base of left and right ventricles; endocardial fibrosis apex left ventricle and base both ventricles; chronic diffuse myocarditis, more severe left ventricle; intimal hyperplasia main branches coronary arteries; hypertrophy media of small intramyocardial arteries; CPC lungs, liver, spleen, kidneys; anasarca

1.730	56 M	CHF 2 years; marked, bilateral enlargement heart; death due to pulmonary embolism; ECG: second degree A-V block, multiple, irregular, polytopic ventricular extrasystoles, abnormal P waves, type IV of RBBB, QS in V_4	HW 500 Gm.; H & D; chronic diffuse myocarditis, aortic arterio-sclerosis (mild); multiple bilateral pulmonary infarcts; splenic and renal infarcts; CPC lungs, liver, spleen, kidneys; anasarca
10 569	27 F	Death, congestive heart failure; ECG: atrial fibrillation, type IV RBBB, qR in V_3, W-shaped in V_4, and rS in V_5	HW 370 Gm.; H & D: small thrombus apex left ventricle without local thinning of cardiac wall; thrombosis right atrial appendage; chronic diffuse myocarditis with areas subacute inflammation, moderate intimal thickening small branches coronary arteries; CPC lungs, liver, spleen, kidneys
11† 417	35 M	CHF 2 years; marked, bilateral enlargement heart; sudden death; ECG: complete A-V block, frequent, polytopic, ventricular extrasystoles, atrial fibrillo-flutter last 3 weeks	HW 490 Gm., H & D; thrombosis apex left ventricle; chronic diffuse myocarditis; moderate artherosclerosis aorta, coronary and cerebral arteries; pulmonary emphysema; old pulmonary and kidney infarcts; area cerebral softening left hemisphere involving temporal lobe; CPC liver, spleen
12 307	38 M	CHF 6 months; ECG: abnormal P waves, polytopic ventricular extrasystoles, incomplete left bundle-branch block	HW 480 Gm.; H & D; thrombosis apex left ventricle with local thinning cardiac wall; thrombosis right atrium; areas fibrous thickening endocardium, apex and base left ventricle, base right ventricle, and right atrium; severe, diffuse, chronic and subacute myocarditis, preponderantly left ventricle; moderate, diffuse, intimal hyperplasia main branches coronary arteries; CPC lungs, liver, spleen, kidneys
13 1.858	39 M	CHF 18 months; marked, bilateral enlargement heart; ECG: abnormal P waves, polytopic ventricular extrasystoles, deep S in V_2 and high R in V_5, V_6, QRS-ST/T changes suggesting recent high anterolateral infarction	HW 500 Gm.; H & D; preponderantly left ventricle; thrombosis at right atrial appendage; chronic myocarditis, preponderantly left ventricle; CPC lungs, liver, spleen, kidneys
14† 184	40 M	CHF 3 years; Adams-Stokes seizures; marked, bilateral enlargement heart; ECG: complete A-V block, ventricular extrasystoles	HW 540 Gm.; H & D; area endocardial fibrosis base of left ventricle; chronic, diffuse and focal myocarditis with granulomatous formations; intimal proliferation of coronary arteries with marked reduction of vascular lumen in some areas, CPC lungs, liver, spleen, kidneys
15† 198	43 M	CHF 20 months; attacks of paroxysmal tachycardia; syphilitic aortitis; marked, bilateral enlargement cardiac shadow, elongation and cylindric dilatation of aortic arch; terminal bronchopneumonia; ECG: multiple, polytopic ventricular extrasystoles, "concordant inverted" type of RBBB, QS in V_4, V_5	HW 640 Gm.; H & D; endocardial fibrosis apex left ventricle with marked thinning of cardiac wall at this area; chronic diffuse myocarditis; myocardium at apex of left ventricle almost completely fibrosed; syphilitic and atherosclerotic lesions of aortic walls; mild intimal hyperplasia main branches coronary arteries; multiple bilateral pulmonary infarcts; bronchopneumonia; bilateral pachypleuritis; CPC lungs, liver, spleen, kidneys
16† 197	45 M	CHF 2 years; marked, bilateral enlargement cardiac shadow; pulmonary tuberculosis; cachexia; ECG: abnormal P waves, polytopic ventricular extrasystoles, concordant type of RBBB, wide and slurred Q deflection in L_2, L_3 (posterior wall necrosis?)	HW 520 Gm.; H & D; endocardial thickening and mural thrombosis at apex and base of left ventricle and apex right ventricle; diffuse thickening of endocardium of right atrium; chronic myocarditis with granulomatous formations; extensive areas of subendocardial fibrosis left ventricle; mild myocardial lesions at atria and outflow tract of right ventricle; mild hyperplasia of intima of main coronary arteries; mild aortic atherosclerosis; caseous pulmonary tuberculosis; miliary tuberculosis of peritoneum, kidneys; CPC lungs, liver, spleen kidneys

TABLE 4.—*Concluded*

Case, reg. no.	Age (years) and sex	Clinical findings	Anatomic findings*
17† 147	50 M	CHF 2 years; grossly irregular heart action with attacks of paroxysmal tachycardia; bilateral enlargement of the heart; chronic malaria; syphilis; aortic atherosclerosis; fibrosis upper lobe right lung (tuberculosis); ECG: atrial fibrillation, multiple, polytopic ventricular extrasystoles, runs of paroxysmal ventricular tachycardia, low voltage of QRST in standard leads, negative T waves in L_2, L_3, low R deflections in left precordial leads, transient, complete RBBB	HW 340 Gm.; H & D; moderate thinning apex left ventricle; chronic myocarditis, with extensive fibrosis particularly in left ventricle; mild aortic atherosclerosis; irregular hyperplasia intima of coronary arteries with severe reduction of lumen; atherosclerotic kidney disease with old infarcts; pulmonary fibrosis (tuberculosis?); CPC lungs, liver, spleen, kidneys; anasarca
18† 2.019	51 M	CHF 3 years; functional tricuspid regurgitation; atypical precordial pains; marked bilateral enlargement of the heart; aortic atherosclerosis; thrombophlebitis of lower extremities; multiple pulmonary embolism; cardiospasm; cachexia; ECG: partial A-V block, notched and widened P waves, type IV of RBBB, delayed R deflections in V_5, V_6, W type of QRS in V_4, multiple, polytopic ventricular extrasystoles, ventricular scapes	HW 500 Gm.; H & D; mural thrombosis apex left ventricle and right atrium; areas endocardial fibrosis at apex and base of left ventricle; thinning of cardiac wall at apex of left ventricle; chronic myocarditis; aortic and coronary atherosclerosis; atheromatous plaque at mitral valve; multiple infarcts at base of both lungs; multiple splenic infarcts; CPC lungs, liver, spleen, kidneys; anasarca; megaesophagus and megacolon
19 249	55 F	CHF 1 year; ECG: atrial fibrillation, polytopic ventricular extrasystoles, low voltage of QRS in standard leads, RBBB, low R deflections in V_5, V_6	Chronic myocarditis with focal and diffuse fibrosis preponderantly left ventricle, CPC lungs, liver, spleen, and kidneys
20† 199	56 M	CHF 3 years; marked bilateral enlargement of heart; aortic atherosclerosis; terminal bronchopneumonia; ECG: polytopic ventricular extrasystoles, abnormal P waves, incomplete RBBB with slurred R and delayed intrinsicoid deflection in V_5, V_6; primary T wave changes (?)	HW 470 Gm.; H & D; preponderantly left ventricle; chronic myocarditis with diffuse fibrosis, preponderantly subendocardial areas of left ventricle; atheromatous plaque at left coronary artery with moderate reduction of the vascular lumen; CPC of lungs, liver, spleen, kidneys; anasarca; bronchopneumonia
21 1.341	58 M	CHF 4 years; moderate enlargement of cardiac shadow, predominantly left ventricle; aortic atherosclerosis; B.P. 140/90; ECG: frequent, polytopic ventricular extrasystoles, "atypical" RBBB, high, slurred R deflections in V_5, V_6, negative T waves from V_1 to V_6	HW 450 Gm.; H & D; preponderantly left ventricle; chronic myocarditis, preponderantly left ventricle; atherosclerosis coronary arteries; mild atherosclerosis renal arteries; chronic diffuse glomerulonephritis; CPC lungs, liver, and spleen

* Fragments from 8 to 14 different areas of the heart were examined.

† Autopsy performed by Dr. Torres and Dr. Duarte, Division of Pathology, Instituto Oswaldo Cruz. In the remaining cases only the heart and fragments of some organs were available for examination.

H W = heart weight; H & D = hypertrophy and dilatation; C P C = chronic passive congestion; C H F = congestive heart failure; Reg. No. = registration number

Complement-fixation test was positive in all cases. Xenodiagnosis was positive in cases 2, 7, 8, 9, 17, 19, 20, and 21; negative, in cases 1, 3, 4, 5, 6, 11, 12, 13, 14, 15, 16, 18.

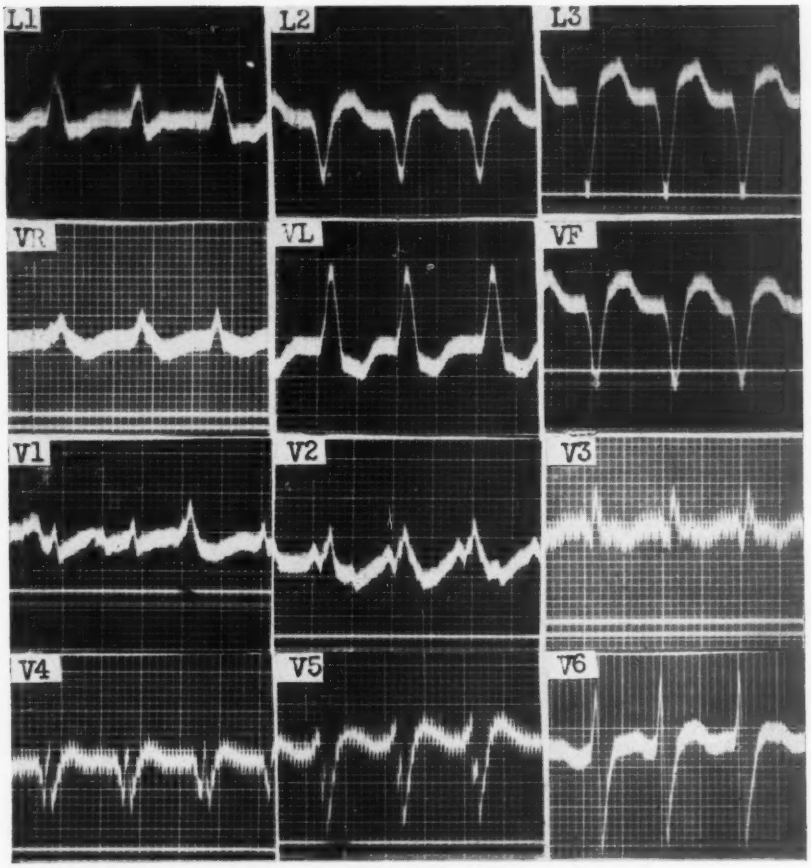

FIG. 12. Right bundle-branch block with qR in V_3, W shaped in V_4, and rS type of QRS in V_5, suggesting anterior necrosis. Case no. 10, table 4. Woman, aged 27. There was no local thinning of the cardiac wall at the apex of left ventricle. The myocardial lesions in this area were not more severe than in other areas of left ventricle.

areas of Chagas' disease, are more commonly associated with chronic Chagas' heart disease.

It may be assumed that a fairly characteristic clinical picture of the cardiopathy with a positive Guerreiro-Machado's reaction constitutes a sound basis for the diagnosis of chronic Chagas' heart disease, despite repeatedly negative results of xenodiagnosis.[13, 15] In 13 out of the 21 cases of chronic Chagas' heart disease proved at autopsy, the diagnosis was made solely on a clinicoserologic basis. In 12 of these cases xenodiagnosis yielded negative results and in some of them repeatedly so. In the remaining 8 patients xenodiagnosis was also positive. Very rarely the complement-fixation test may be negative and the xenodiagnosis may yield positive results.

In its early stages, chronic Chagas' heart disease, in patients under 20 years of age, may be difficult to differentiate from rheumatic carditis. Loud systolic murmurs due to functional mitral or tricuspid regurgitation in some cases of chronic Chagas' heart disease with advanced heart failure may lead to an erroneous diagnosis of valvular heart disease. Coronary heart disease is the most difficult problem in differential diagnosis. Chronic Chagas' heart disease occurs in the younger age groups,

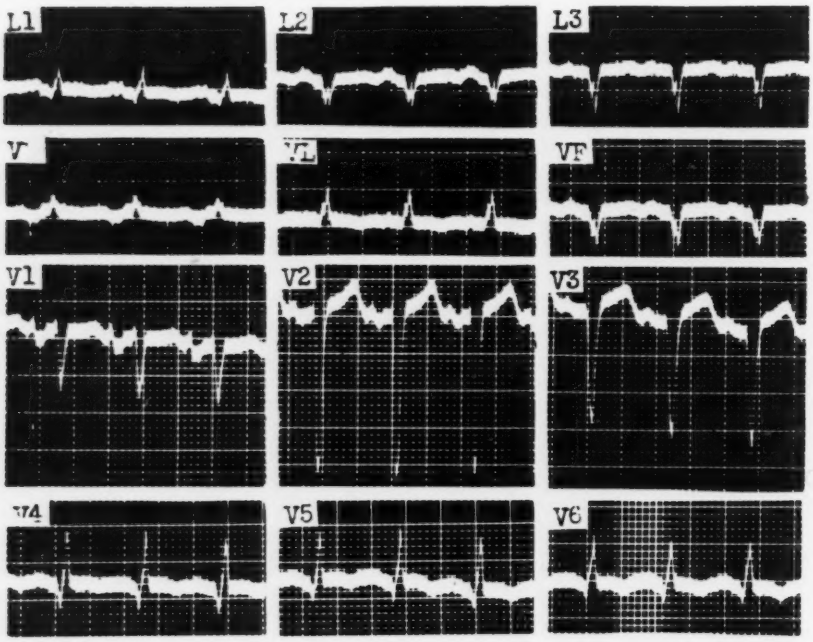

FIG. 13. QRST changes without bundle-branch block. Case no. 6, table 4, aged 26. Marked left axis deviation, deep S in V_2, slurred QRS with delayed intrinsicoid deflection in left precordial leads, suggesting left ventricular enlargement. QS in L_2, L_3, and V_F, suggesting posterior necrosis. QS in V_3 and qR from V_4 to V_6, with ST-T changes, suggesting anterolateral infarction. There were severe chronic and subacute diffuse myocarditis with endocardial fibrosis and mural thrombosis at apex of left ventricle. The main coronary arteries were patent and no myocardial infarction was found.

the patients do not complain of the typical precordial pain; the acute, transient injury changes of the electrocardiogram are not common. In age groups over 50, coronary atherosclerosis is commonly associated with chronic Chagas' heart disease. High blood pressure is unusual in patients with chronic Chagas' heart disease.

At the present stage of our knowledge it seems reasonable to assume that in countries where Chagas' disease exists in an endemic form, such diagnoses as Fiedler's myocarditis, chronic myocarditis of unknown etiology, or myocardial disease of unknown cause should not be made unless Chagas' disease has been adequately excluded as a possible etiologic factor.

Clinical Course and Prognosis

As a rule the heart lesions of chronic *S. cruzi* infection develop and progress slowly. Even after the manifestations of heart failure the patient may survive for a long time. Most cases exhibit several bouts of congestive heart failure until the condition finally becomes irreversible.

In some patients, usually under 30 years of age, the heart condition presents a brief, more severe course. Heart failure supervenes earlier and has no tendency to reversion. There are gross irregularities of cardiac rhythm (ventricular extrasystoles, ventricular tachycardia, atrial fibrillation) and abnormalities of QRS or T waves, without advanced heart block; death is due to congestive heart failure, usually with pulmonary embolism. In the myocardium there are acute and chronic inflammatory lesions; the fibrotic lesions are less marked and *S. cruzi* is usually found with less difficulty (cases 1, 4, and 6, table 4). Such cases could be classified as subacute Chagas' heart disease.

Approximately 55 per cent of the fatal cases

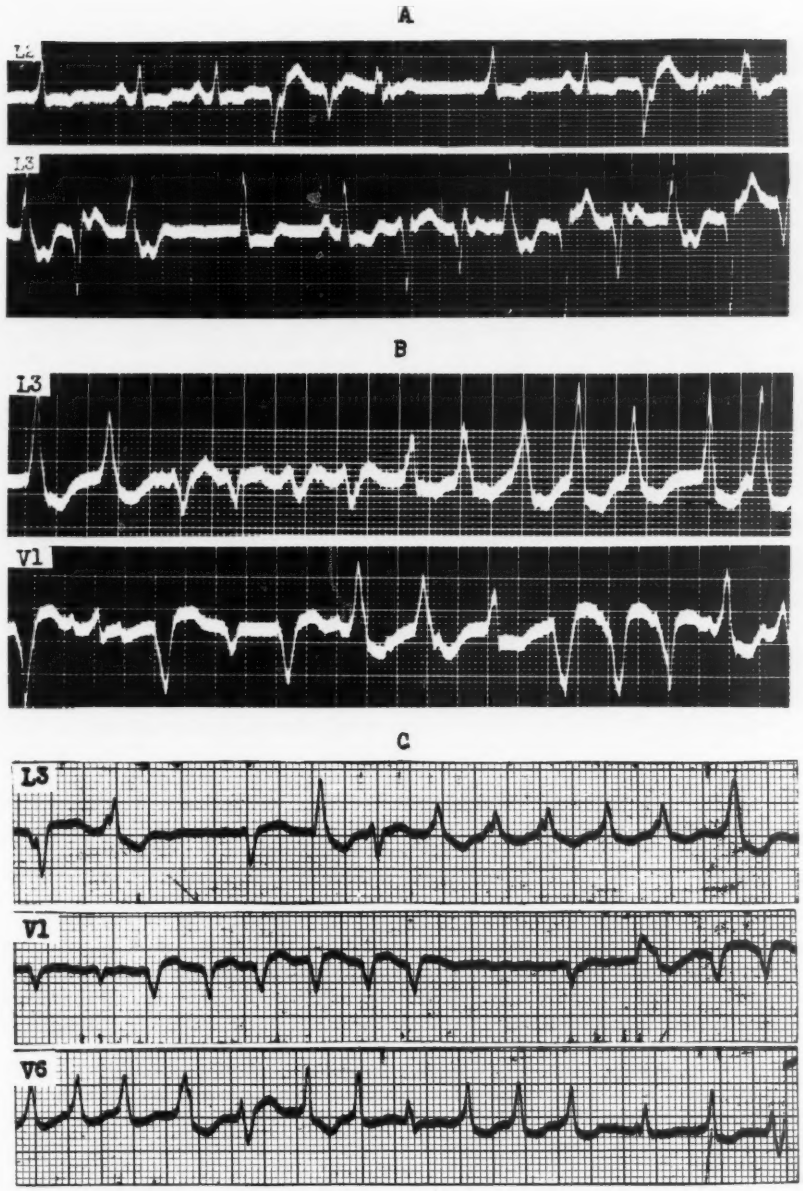

FIG. 14. Complex arrhythmias resulting in chaotic heart action. *A*. Case no. 4, table 4. Woman aged 20. Sinus rhythm; atrial rate 106. P-R = 0.16 sec. Multiple, polytopic premature ventricular contractions, forming bouts of extrasystolic ventricular tachycardia. The patient received small doses of digitalis; ectopic contractions disappeared with discontinuance of the drug. Record made 27 days before death of the patient. *B*. Case no. 1732. Man, aged 47. Atrial tachycardia, rate 187. Bouts of extrasystolic ventricular tachycardia. Record made 3 days before death of the patient. *C*. Case no. 2197. Woman, aged 38. Atrial fibrillation with runs of probably ectopic ventricular contractions (or transient left bundle-branch block of variable degrees?).

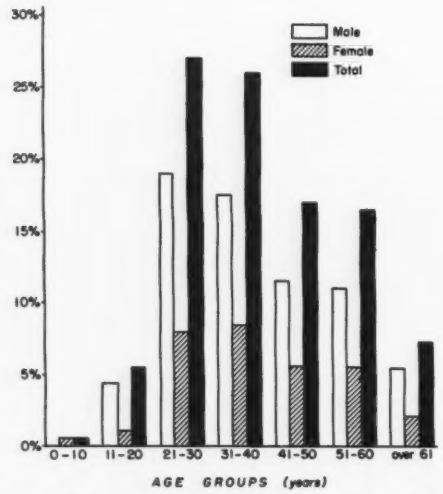

FIG. 15. Age and sex distribution of 200 fatal cases of chronic Chagas' heart disease.

are in the age groups 21 to 40 (fig. 15). Mortality is low in patients up to 20 years of age.

Prognosis is difficult. Sudden and unexpected death is very common in this cardiopathy. Patients with moderately advanced heart damage and without heart failure may die unexpectedly. Complete A-V block, some types of right bundle-branch block, frequent, polytopic ventricular premature contractions, ventricular tachycardia, QRS abnormalities suggesting an area of myocardial necrosis, marked enlargement of the heart, and signs of heart failure are of severe prognostic significance.

Pathology

The cardiac lesions of Chagas' disease were initially described by Vianna,[29] Chagas,[5, 6] Torres,[26-28] and Mazza[19-21] in fatal cases of American trypanosomiasis. The chief anatomic findings included enlargement of all the cardiac cavities; hypertrophy of the heart; a diffuse inflammatory process of the myocardium (occasionally involving the parietal endocardium[28] with diffuse fibrosis and infiltration by lymphocytes, macrophages, and plasma cells, and in some cases eosinophils and polymorphonuclear neutrophils; areas of waxy degeneration of myocardial fibers and the presence of leishmanial forms of *S. cruzi* in myocardial fibers. The condition has been described[5, 6] as an isolated myocardial disease, without involvement of the valvular endocardium or the large vessels.

The number of published autopsy cases of chronic Chagas' heart disease with the presence of *S. cruzi* in the myocardium is small. The pathologic picture of this condition is still only incompletely known.

The chief clinicoanatomic findings in our series of 21 cases with the presence of *S. cruzi* in myocardial fibers are shown in table 4:

1. Heart weight was increased in all cases. Dilatation of all cardiac cavities was pronounced in most cases, particularly the right ventricle and the right atrium. Left ventricular thickness exceeded 15 mm. in 2 cases.

2. Circumscribed areas of endocardial fibrosis (fig. 16*A*) in the left ventricle were present in 15 cases, its localization being as follows: apex 8 cases, base 3 cases, apex and base 4 cases. In 3 of these cases there was also endocardial fibrosis at the apex (1 case) or base (2 cases) of the right ventricle.

Mural thrombus in different stages of organization (fig. 16*B*) at the apex of left ventricle was found in 11 cases. In 7 cases a circumscribed area of thinning of the apical portion of the left ventricle, constituting a pseudoaneurysm of the apex, was present. Mural thrombus at the right atrium or right atrial appendage was found in 7 cases, with endocardial fibrosis in 5.

3. A disseminated inflammatory process of the myocardium (fig. 16*C*) involving all the cardiac walls and septum, sometimes extending to the parietal endocardium, was found in all the 21 cases.

The cellular infiltration was diffuse and focal and consisted chiefly of lymphocytes, plasma cells, and macrophages; eosinophils and polymorphonuclear neutrophils were also present. In 4 cases the myocarditis could be classified as subacute (cases no. 4, 6, 10, 12). A "granulomatous form" of myocarditis was present in 5 cases (no. 4, 5, 11, 14, 16). Collections of lymphocytes and plasma cells in the epicardium (fig. 16*D*) were seen in some cases.

Focal and diffuse fibrosis of the myocardium was present in all cases, its intensity varying in different cases and in the same case from one

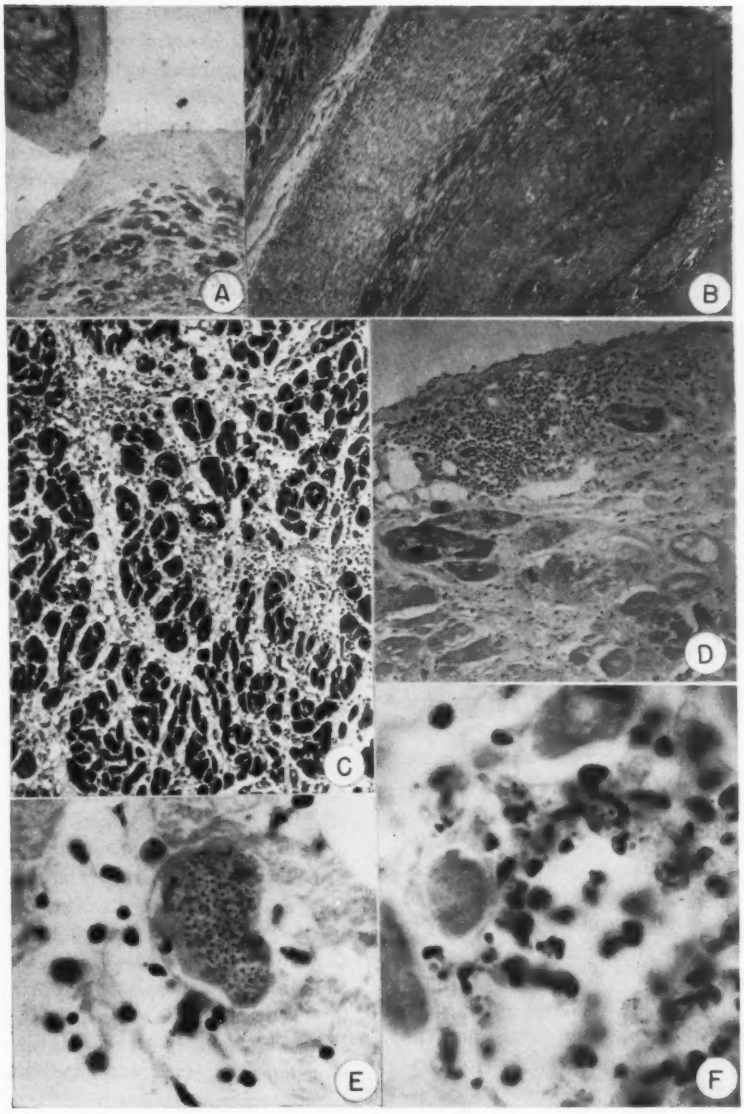

FIG. 16. Heart sections from patients with chronic Chagas' heart disease (table 4).

A. Case no. 1. Endocardial fibrosis. Note myocardial fibrosis at subendocardial areas (Masson stain × 54). *B*. Case no. 16. Endocardial fibrosis and mural thrombosis in different stages of organization at apex of left ventricle (Masson stain × 54). *C*. Case no. 6. Diffuse infiltration and fibrosis of myocardium. This aspect is seen in most sections of myocardium in cases of chronic Chagas' heart disease (H & E × 112). *D*. Case no. 8. Collection of lymphocytes, macrophages, and plasma cells in epicardium (H & E × 112). *E*. Case no. 4. A transverse section of a myocardial fiber containing leishmanial forms of *S. cruzi*. *F*. Case no. 4. Leishmanial forms of *S. cruzi* in myocardium phagocyted by macrophages. Some polymorphonuclear cells are seen in the cellular exudate.

area to another. Fibrosis was conspicuously more severe in the left ventricle followed in order of frequency by the right ventricle and the right atrium. The less severe lesions were found in the left atrium. In 3 cases (no. 1, 16, 20) the fibrosis in the left ventricle was preponderantly subendocardial.

Leishmanial forms of *S. cruzi* in myocardial fibers (fig. 16*E*) were found in all the 21 cases; occasionally the parasite may be seen phagocyted by macrophages (fig. 16*F*). In 3 cases the parasite was found without difficulty on microscopic examination of the heart; in the remaining cases a time-consuming search was necessary. In no case was *S. cruzi* found in any other tissue but the myocardium.

4. Aortic and coronary atherosclerosis was conspicuous in the majority of the patients over 40 years of age. In some of them severe reduction of the lumen of the coronary arteries was present; in others the atherosclerotic lesions were mild.

Obliterative changes of the small and medium-sized branches of coronary arteries, with reduction of the vascular lumen, were present in various cases in the younger age groups. Thickening of the intima and edema or hypertrophy of the media was present in such cases.

Venous congestion and dilatation of capillaries, sometimes with extravasation of red blood cells into the myocardium, were found in most cases. Large thin-walled blood vessels, particularly in areas of extensive myocardial fibrosis, occasionally were observed.

5. Myocardial ischemia is probably an important mechanism in the development and progression of chronic Chagas' heart disease. In the enlarged heart, the vascular lesions and the dynamic factors usually operating in this condition (reduced systolic and pulse pressures, diminution of the capacity of the myocardium to raise systolic pressure, occurrence of frequent ectopic inefficient contractions) may result in coronary insufficiency. Local endocardial thickening, disturbed myocardial nutrition through the Thebesian vessels, and blood stagnation in the venous vessels of the heart have been claimed[1] to play major roles in the production of the ischemic myocardial lesions.

Treatment

No drug has yet been found to be entirely effective against *S. cruzi* infection. A 4-aminoquinoline derivative* and a sulfurated arsenobenzol† are claimed[2] to possess trypanocidal effects on the circulating forms, but not on the intracellular forms of *S. cruzi* and to exert favorable effects on the evolution of some manifestations of the acute infection. Trials on experimentally infected dogs seem to show that a sulfurated arsenobenzol derivative‡ may destroy the blood forms of *S. cruzi* but does not prevent the development of chronic heart disease in these animals.[16] Various other drugs have been tested[16] without encouraging results.

Summary and Conclusions

Triatomid bugs, infected with *Schizotrypanum cruzi*, are widely distributed in this hemisphere, extending from the United States to Argentina. Our knowledge of the incidence and severity of human infection with *S. cruzi* in most of the large endemic areas is still incomplete. In the present state of our knowledge, Chagas' disease should be considered as an essentially cardiotropic infection, caused by *S. cruzi*, having an acute period with multiple, reversible manifestations due to involvement of various tissues and organs. The heart is affected in the majority of cases. A prolonged chronic course follows, with late manifestations of progressive heart involvement (chronic Chagas' heart disease). There is no definite proof as yet whether esophageal involvement (cardiospasm), which occurs so frequently in some endemic areas of Chagas' disease, is related to chronic *S. cruzi* infection.

Acute Chagas' heart disease may be defined as a reversible type of parasitic heart disease, caused by acute *S. cruzi* infection, occurring predominantly in infancy and childhood and anatomically characterized by an acute, diffuse, usually severe, specific myocarditis that eventually leads to heart failure without conspicuous irregularities of the cardiac rhythm.

* 7602 (Ac), Bayer
† 9736 (As), Bayer
‡ Spirotrypan (Farbwerke-Hoechst AG.)

Our present concept of chronic Chagas' heart disease is that of a progressive, usually severe type of heart disease, related to chronic *S. cruzi* infection, preponderantly affecting males in the 20- to 50-year age groups, manifested clinically by the almost constant occurrence of disturbances in the formation and conduction of the cardiac stimulus and by congestive heart failure. Anatomically widespread inflammatory changes of the myocardium are usually accompanied by circumscribed lesions of the parietal endocardium and by slowly developing ischemic myocardial changes.

Summario in Interlingua

Scarabeos del genere *Triatoma*, inficite con *Schizotrypanum cruzi*, se trova extensemente distribuite in le Americas inter le Statos Unite e Argentina. Nostre cognoscentias del incidentia e del severitate de infectiones de humanos con *S. cruzi* in le majoritate del grande areas endemic es ancora incomplete. Super le base de nostre cognoscentias currente, morbo de Chagas debe esser considerate como un infection essentialmente cardiotropic, causate per *S. cruzi*, e characterisate per un periodo acute con multiple revertibile manifestationes que resulta del implication de varie histos e organos. Le corde es afficite in le majoritate del casos. Il seque un prolongate curso chronic, con tardive manifestationes de un progressive implication del corde (chronic morbo cardiac de Chagas). Il existe non ancora ulle prova definite que le implication esophagee (cardiospasmo), que occurre si frequentemente in certe areas endemic de morbo de Chagas, es connectite con infection chronic per *S. cruzi*.

Acute morbo cardiac de Chagas pote esser definite como un typo revertibile de parasitic morbo cardiac, causate per acute infection per *S. cruzi* occurrente predominantemente in infantes e juveniles, e characterisate anatomicamente per un acute, diffuse, e usualmente sever myocarditis specific que resulta in le curso del tempore in disfallimento cardiac sin conspicue irregularitates del rhythmo cardiac.

Nostre currente concepto de chronic morbo cardiac de Chagas es le concepto de un progressive e usualmente sever type de morbo cardiac, connectite con infection chronic per *S. cruzi*, afficiente preponderantemente masculos del gruppos de etate inter 20 e 50 annos, e manifeste clinicamente per le quasi constante occurrentia de disturbationes in le formation e le conduction del stimulo cardiac e per congestive disfallimento cardiac. Anatomicamente extense alterationes inflammatori del myocardio es usualmente accompaniate per circumscripte lesiones del endocardio parietal e per le lente disveloppamento de ischemic alterationes myocardial.

REFERENCES

1. Andrade, Z. A., and Andrade, S. G.: A patologia da doença de Chagas. Bol. da Fundação Gonçalo Moniz **6:** 1, 1955.
2. Chagas, C.: Aspecto clinico da nova entidade morbida produzida pelo Schizotrypanum cruzi. Brasil-méd. **24:** 263, 1910.
3. —: Nova entidade morbida do homem. Resumo geral dos estudos etiológicos e clínicos. Mem. Inst. Oswaldo Cruz **3:** 219, 1911.
4. —: Tripanosomiase Americana. Forma aguda da moléstia. Mem. Inst. Oswaldo Cruz **8:** 37, 1916.
5. —: Processos patogênicos da trypanosomiase americana. Mem. Inst. Oswaldo Cruz **8:** 7, 1916.
6. —: Sur les altération du coeur dans la trypanosomiasis americaine (Maladie de Chagas). Arch. mal. coeur **21:** 641, 1928.
7. —, and Villela, E.: Forma cardiaca da trypanosomiase americana. Mem. Inst. Oswaldo Cruz **14:** 5, 1922.
8. Dias, E.: Chagas-Krankheit (Chagas' disease). Welt-Seuchen Atlas. Hamburg, Falk Verlag, 1954, Vol. II, p. 135.
9. —: Doença de Chagas nas Américas. I-Estados Unidos. Rev. Brasil. malariol. **3:** 448, 1951.
10. —, Laranja, F. S., and Nobrega, G.: Doença de Chagas. Mem. Inst. Oswaldo Cruz **43:** 495, 1945.
11. — and Laranja, F. S.: Chagas' disease and its control. Fourth Intern. Cong. Trop. Med. and Mal. Washington, Proceed. **2:** 1159, 1948.
12. Laranja, F. S., Dias, E., and Nobrega, G.: O electrocardiograma na cardiopatia cronica da doença de Chagas. Mem. II Cong. Interam. Cardiol., Mexico **3:** 1470, 1946.
13. —, —, and —: Clínica e terapêutica da doença de Chagas. Mem. Inst. Oswaldo Cruz **46:** 473, 1948.
14. —, Pellegrino, J., and Dias, E.: Experimental Chagas' heart disease. Abstracted, Am. Heart J. **37:** 646, 1949.
15. —: Evolução dos conhecimentos sôbre a cardiopatia da doença de Chagas. Revisão crítica da

literatura. Mem. Inst. Oswaldo Cruz **47:** 605, 1949.

[16] —: Aspectos clínicos da moléstia de Chagas. Rev. brasil. med. **10:** 482, 1953.

[17] —, Dias, E., and Pellegrino, J.: Chagas' heart disease: a cardiological entity. Ier. Congress Mondial de Cardiologie. Paris, 1950. Resumès, p. 302.

[18] —, —, —, and Duarte, E.: Observações clínicas epidemiológicas sôbre a moléstia de Chagas no Oeste de Minas. O Hospital **40:** 945, 1951.

[19] Mazza, S.: La enfermedad de Chagas en la Rep. Argentina. Mem. Inst. Oswaldo Cruz **47:** 273, 1949.

[20] —, Basso, G., Basso, R., and Jorg, M. E.: Primer caso mortal de forma cronica cardiaca de enfermedad de Chagas, comprobada en Mendoza. Misión estud. pat. reg. Argent. **42:** 3, 1939.

[21] —, and Jorg, M. E.: Diferencias entre anatomia patologica carditis reumatica y carditis de enfermedad de Chagas. Misión estud. pat. reg. Argent. **42:** 79, 1939.

[22] —, Basso, G., and Basso, R.: Ensayos terapeuticos del producto 9736 (As), Bayer, y de su acción comparada con el 7602 (Ac) Bayer en la enfermedad de Chagas. Misión estud. pat. reg. Argent. **61:** 3, 1942.

[23] Pedreira de Freitas, J. L.: Contribuição para o estudo do diagnóstice da moléstia de Chagas por processos de laboratorio. Tese de doutoramento. Fac. Med. Univ. de São Paulo, 1947.

[24] Muniz, J.: Do valor da reação de precipitina no diagnóstico das formas agudas e sub-agudas da doença de Chagas. Brasil-méd. **29:** 261, 1947.

[25] Romaña, C.: Acerca de un sintoma inicial de valor para el diagnóstico de forma aguda de la enfermedad de Chagas. La conjuntivitis esquizotripanosica unilateral (hipotesis sobre puerta de entrada conjuntival de la enfermedad) Misión estud. pat. reg. Argent. **22:** 16, 1935.

[26] Torres, C. B. M.: Estudo do miocardio na moléstia de Chagas (forma aguda). Alteração da fibra muscular cardiaca. Mem. Inst. Oswaldo Cruz **9:** 114, 1917.

[27] —: Patogenia de la miocarditis crónica de la enfermedad de Chagas. V Reun. Soc. Arg. Patol. Reg. del Norte, 1930, p. 902.

[28] —: Endocarditis parietale dans la maladie de Chagas (Trypanosomiase americaine). C. R. Soc. Biol. **99:** 886, 1928.

[29] Vianna, G.: Contribuição para o estudo da anatomia patológica da moléstia de Carlos Chagas. Esquizotripanose humana ou Tireoidite parasitaria. Mem. Inst. Oswaldo Cruz **3:** 276, 1911.

Following his marriage Withering began to cast about for a more profitable practice since his income did not exceed £100 a year. When, therefore, he received an unexpected letter in February of 1775 from Erasmus Darwin telling him of the death of Dr. Small of Birmingham and suggesting that there was thus a good opening for a competent young practitioner in the busy Midland metropolis, he accepted the proposal with enthusiasm. Later in the year he was appointed a junior assistant to Dr. John Ash of the General Hospital. He started in practice in May and moved his family to Birmingham later in the year.

Withering's success in his new environment was immediate. Not only was he taken into social and intellectural circles, but his practice quickly grew to one bringing in an income of £1000 a year, later £2000, an enormous sum for those days—and this despite the fact that he held a daily free clinic for the poor at the General Hospital and is said to have treated three thousand cases annually without charge. He was sought as a consultant from all over the Midland and western counties. He also began to conduct a huge correspondence with distinguished personages who wrote for medical counsel. One such request came from Paris from no less a person than Benjamin Franklin who sought advice about treating his "bladder stone."

In the year 1785 Withering made a record of the distances he had travelled for consultation and found that it added up to 6,303 miles—not far perhaps for these days, but for the horsedrawn vehicles and bad country roads of the eighteenth century it was an astonishing feat. But the time was not wasted, for he occupied himself during his long journeys in making his clinical notes and examining specimens of his plants and minerals.—John F. Fulton. *The Place of William Withering in Scientific Medicine.* J. Hist. Med. & Allied Sc., **8:** 8, 1953.

Acute and Chronic Cardiovascular Effects of Pentolinium in Hypertensive Patients

By JOSEF R. SMITH, M.D., AND S. W. HOOBLER, M.D.

Using a tracer injection technic, modified to provide accurate and repeated determinations of cardiac output in the ambulatory patient, the authors have shown that chronic pentolinium therapy for hypertension lowers blood pressure by reducing cardiac output in the seated position. From these observations and the work of others, they believe that the effect of ganglionic blockade on venoconstrictor tone deserves greater emphasis.

DESPITE the widely accepted use of ganglionic-blocking agents in the treatment of severe hypertension, surprisingly little is known of the mechanism whereby the blood pressure is reduced in the ambulatory patient. In particular, it has not been possible heretofore to make repeated observations of the effect of these agents on the cardiac output in the orthostatic hypertensive patient before and at various time intervals following initiation of treatment. This report deals with certain modifications of the dye injection method for cardiac output, which permits such repeated examinations, and is, to our knowledge, the first study of the effect of chronic pentolinium* treatment on the cardiac output and peripheral resistance in hypertensive patients.

METHODS

Patients studied were those with severe essential hypertension (blood pressures of 186–225/117–129). The cardiac output was performed in the seated position. The dye-dilution method of Stewart and Hamilton[1-5] as modified by Pritchard and his group[6] for the use of iodinated serum albumin (RISA) was the basic principle used in measuring cardiac output, except that arterial samples were collected in tubes rather than passed through the counting device they describe. Pritchard's method was further modified as follows: 1. The RISA-containing syringe was weighed before and after injection to determine accurately the quantity of isotope injected. 2. A flushing syringe containing 10 ml. of normal saline was attached by a T connection and a 1-way valve to propel more rapidly the bolus of injected substance. 3. Individual brachial artery samples were collected every 2 sec. by means of a circular test tube rack placed on a simple rotating stool and moved by hand, in time with the clicks of a metronome set at 60 beats/min. 4. Representative samples were pipetted into radioactively clean test tubes and counted individually in an iodine crystal-type well scintillation counter.* The measured samples were compared to known dilutions of the stock RISA solution injected. Each sample and standard was counted for 6400 or more counts, which gives a theoretical counting error of 1.25 per cent or less in each sample. The cardiac output was calculated from Hamilton's formula,[5] the curves being plotted on semilogarithmic paper extrapolated to 0 to exclude recirculated test substance. The formula used was

$$\text{Cardiac output (L./min.)} = \frac{\text{Total counts injected} \times 60}{\text{Sum of counts/sec./ml. at each 1 sec. interval as determined under the extrapolated curve}} \times \frac{1}{1000}$$

Mean circulation time was calculated from the formula,

$$MCT = \frac{\sum (C \cdot t)}{\sum C},$$

where C equals the counts per second at the time t and t equals the time interval (in seconds) from the time of injection to the time at which concentration

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Dr. Smith is a Research Fellow of the Michigan Heart Association.

We are indebted to Dr. Daniel Shaw of Wyeth & Company for the supply of pentolinium used in these studies.

* We wish to express our appreciation for the kind cooperation of Dr. William Beierwaltes and of Dr. Philip Johnson and the staff of the Isotope Unit of the University Hospital for their valuable assistance in this project.

was measured. Using these figures, pulmonary blood volume was calculated from the formula,

$$PBV = \frac{\text{Cardiac output (ml./min.)}}{60} \times MCT$$

as described by Hamilton and associates.[3] Mean blood pressure at the time of the determination was calculated as the diastolic pressure plus $\frac{1}{3}$ of the pulse pressure. The reading represented the average of readings just before and just after injection of the tracer solution. Total peripheral resistance was calculated from the formula

$$TPR \text{ (dynes cm.}^{-5} \text{ sec.)} = \frac{MBP \times 1332 \times 60}{\text{Cardiac output (ml./sec.)}}$$

$$\text{Cardiac index was calculated as } \frac{\text{Cardiac output}}{\text{M.}^2 \text{ Surface area}}.$$

Initial determinations, done 20 min. apart before therapy, gave an average variation in the cardiac output of ±3.29 per cent with an upper limit of 6.75 per cent. The average value was 2.84 L./M²/min. This is somewhat low, but the standing cardiac output was found to be decreased 33 per cent by McMichael and Sharpey-Schafer[7] and a similar decrease would also be expected on sitting. Cardiopulmonary blood volume measurements varied up to ± 7.1 per cent with an average of ± 4.1 per cent. Although this measurement is considered rather inaccurate by Hamilton and others,[3] a study by Doyle and co-workers[8] gives figures on variation that are consistent with our data. Because precision is essential in obtaining reproducible results by this modified method for cardiac output, the following typical experiment is presented in some detail.

Experiment

E. L. P. was placed in the seated position, a 19-gage needle was inserted into the antecubital vein, and the arm elevated on pillows to heart level. An 18-gage Cournand arterial needle was inserted in the brachial artery of the opposite arm, and a Decholin circulation time was determined at 10.6 sec., which indicated the probable range of collection time for the subsequent arterial samples. After a few minutes to achieve a steady state, her brachial blood pressure, determined by an aneroid sphygmomanometer, was found to be 208/124. A known amount of RISA, approximately 10 microcuries in 2–3 ml., was injected in less than 1 sec. through the venous needle and was flushed rapidly into the central venous reservoir by the injection of 10 ml. of normal saline. A 3 sec. time lag (7 sec. less than the Decholin circulation time) was allowed and then collections were made from the Cournand needle through a $\frac{1}{16}''$ internal diameter siliconized plastic tubing and a special 3-way stopcock bored out to $\frac{3}{32}''$. The flow was manually directed to a new tube every 2 sec. and a total of 24 samples were collected in tubes containing dried heparin. Individual samples averaged 1.2–2.0 ml. A specimen for blood volume was collected from the arterial needle 10 min. after the injection. The procedure was repeated 20 min. after the injection with the patient remaining in the same position and with a second dose of RISA containing the same amount of activity. The patient was then given 8 mg. of pentolinium bitartrate through the intravenous needle in divided doses over a period of 25 min. until her blood pressure had fallen to 106/70. The cardiac output was then repeated twice at 10 to 20 min. intervals; 2 and 4 times the radioactivity of the original sample were used to insure a new level significantly above background. The patient was then placed on oral pentolinium treatment and satisfactory blood pressure control was achieved. Ten days after the original determination, another set of duplicate determinations was done in the sitting position at the time of a significant blood pressure reduction. The method described delivered radiation of less than 0.1 millicurie of I^{131} to the patient, a dose that is considered well within the safe range.

Using the isotope, one can perform multiple determinations without staining the skin as would occur if Evans-blue had been used as the tracer substance. Collecting specimens in tubes and using a well-type scintillation counter provided greater accuracy and a lower total radiation dose as well as avoiding the special equipment required by Pritchard's technic.[6]

The acute effects of pentolinium bitartrate were studied in this manner in 5 severely hypertensive patients, 4 of whom were subsequently re-examined after 6 to 128 days on oral treatment. Two additional patients, G. Na. and G. Be. were studied before and after chronic treatment but were not observed after acute intravenous injection of the drug. Finally, 1 patient, M. Po., who had been on therapy approximately 1 year, had the opposite procedure, i.e., a determination while on therapy and a second one after treatment was stopped and the blood pressure had risen to pretreatment levels (table 1, fig. 2).

Results

Reductions in blood pressure following acute therapy ranged from 54/17 to 145/63 mm. of Hg, or from 31 to 90.3 mm. of mean blood pressure. This change corresponds to an average blood pressure fall of 36.8 per cent with a range from 22 to 57 per cent. Chronic studies revealed blood pressure falls from 10/9 to 76/42. Expressed as per cent fall in mean blood pressure, the average was 24 per cent with a range from 6 to 45 per cent (table 1, fig. 1).

Values for cardiac index fell in all patients,

TABLE 1.—*Hemodynamic Changes Following Acute Intravenous and Chronic Oral Pentolinium*

Patient	Observation	Blood pressure			Mean circulation time	Cardiac index		Stroke volume		Peripheral resistance		Pulmonary volume	
		Systolic/diastolic mm. Hg	Mean	% Δ	sec.	L./M.²/min.	% Δ	ml.	% Δ	dynes/sec./cm.⁻⁵	% Δ	ml.	% Δ
L. Ke.	Initial	204/121	145		19	2.94		52.4		2631		1365	
	Acute-1	110/80	90	−38	21	1.65	−44	28.8	−45	2910	11	848	−38
	Acute-2	128/84	99	−32	21	2.03	−31	38.1	−27	2591	−1	1049	−23
	Chronic-1	180/106	131	−10	20	2.30	−22	45.5	−13	3018	15	1185	−13
	Chronic-2	176/110	132	−9	18	2.29	−22	45.2	−14	3069	17	1038	−24
La. P.	Initial	200/117	148		19	3.24		63.4		1943		1918	
	Acute-1	106/70	82	−45	28	1.57	−51	35.2	−44	2215	14	1401	−27
	Acute-2	146/100	115	−22	22	2.32	−28	49.6	−22	2106	8	1622	−15
	Chronic-1	152/96	115	−22	22	2.27	−30	59.2	−7	2151	11	1584	−17
	Chronic-2	150/92	111	−25	21	2.43	−25	60.1	−5	1947	0	1569	−18
C. Na.	Initial	211/119	150		24	2.97		79.1		1995		2412	
	Rx 6 days	152/96	105	−30	39	1.86	−37	58.6	−26	2239	12	2436	1
G. Fa.	Initial	214/129	158		18	3.42		72.7		1995		2016	
	Acute-1	142/98	113	−29	25	2.31	−32	48.5	−33	2110	6	1750	−13
	Acute-2	138/90	106	−33	26	2.30	−33	48.3	−34	1992	0	1828	−9
	Chronic-1	150/108	122	−23	27	1.80	−47	41.7	−43	2920	46	1508	−25
	Chronic-2	160/106	124	−21	26	2.50	−27	56.4	−22	2143	7	1988	0
H.v A.	Initial	186/119	141		38	2.25		54.8		2572		2795	
	Acute-1	130/96	110	−22	34	1.84	−18	42.6	−22	2456	−4	2045	−27
	Chronic-1	176/110	132	−6	28	2.16	−4	52.3	−5	2521	−2	927	−31
	Chronic-2	174/110	132	−7	32	2.00	−11	48.4	−12	2716	6	2067	−26
G. Be.	Initial	196/124	148		16	3.28		47.3		2502		1266	
	Chronic-1	100/72	81	−45	25	2.07	−37	33.8	−28	2185	−13	1251	−1
	Chronic-2	108/74	85	−42	32	1.94	−41	32.5	−31	2438	−3	1508	19
	Chronic-3	120/82	95	−36	25	2.79	−15	47.9	1	1883	−25	1689	33
	Chronic-4	120/82	95	−36	27	2.98	−9	51.0	8	1765	−29	1902	50
G. Go.	Initial	225/123	157		24	2.12		39.7		3626		1409	
	Acute-1	98/62	74	−53	40	1.03	−51	19.0	−52	3531	−3	1125	−20
	Acute-2	80/60	67	−57	30	1.31	−38	25.3	−36	2517	−31	1079	−23
M. Po.*	Chronic	157/106	123		31	2.00		53.5		2665		1877	
	Off Rx.	200/122	148	17	35	2.89	44	69.9	31	2262	−15	3143	67

* M. Po. was first tested while on chronic treatment. Three days after withholding the drug, the observation was repeated.

All procedures were done in seated posture. "Initial" determinations are the average of 2 determinations done in the pretreatment state. "Acute" observations were done 20 min. apart after the blood pressure had fallen significantly following intravenous injection. "Chronic" were also paired observations after varying periods of oral therapy.

both in the acute and chronic studies. In the acute studies, the cardiac indices fell from 0.41 to 1.67 L./min., giving an average percentage fall of 37.3 per cent. After prolonged treatment an average decrease of 25.2 per cent was observed. In all but 1 instance, G. Be., the reduction in cardiac index paralleled the reduction in blood pressure. Since pulse rate did not change markedly, it follows that there was a comparable decrease in stroke volume. In the acute observations, the average reduction was 35 per cent and ranged from 22 to 52 per cent. In chronic studies the average reduction was 15.1 per cent with a range from +8 to −43 per cent.

Calculation of peripheral resistance gave figures averaging 2,553 dynes/cm.$^{-5}$ before treatment. After acute blood pressure reduction, the average peripheral resistance was 2,492 dynes/cm^{-5} or a fall of 2.4 per cent. In the chronic studies, there was an average rise in peripheral resistance of 4.9 per cent. It will be

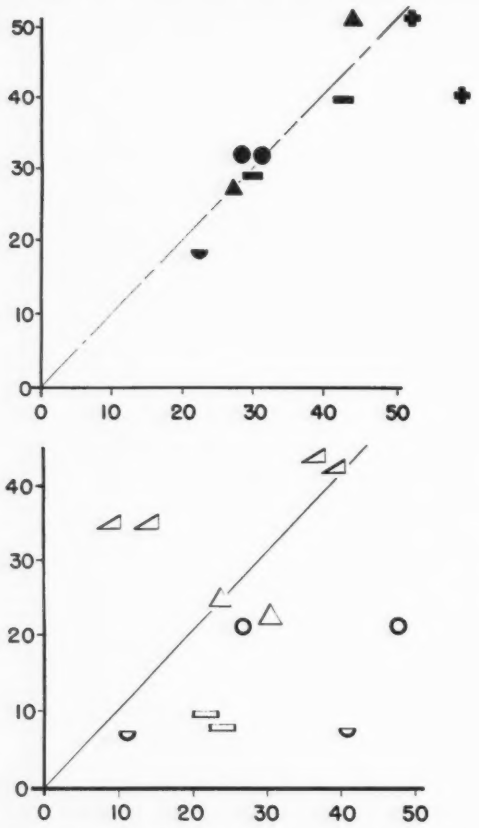

FIG. 1. *Top*. Effect of intravenous pentolinium on blood pressure and cardiac output in sitting position. *Bottom*. Effect of chronic oral pentolinium therapy on blood pressure and cardiac output in sitting position. Ordinate, per cent fall in mean blood pressure; abscissa, per cent fall in cardiac index.

Points falling on the diagonal lines represent instances in which cardiac output and blood pressure fell equally (peripheral resistance unchanged); points above and below are cases in which peripheral resistance fell or rose when compared to the average of 2 determinations in the initial (untreated) state. The symbols represent the results of each of a pair of determinations on each patient and the block symbols in the *bottom* correspond to the same patients in the *top*. In the acute study little change in peripheral resistance occurred, while in the chronic study there was a wider scatter with a tendency for the peripheral resistance to increase.

noted that only 2 patients in the acute study and 1 in the chronic study (G. Be.) experienced any significant fall in peripheral resistance. The latter was examined on 2 occasions while

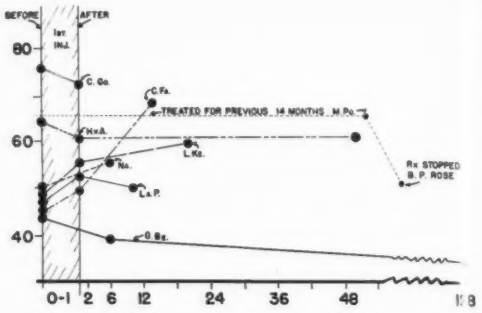

FIG. 2. Effect of chronic oral administration of pentolinium on peripheral resistance in sitting position.

The peripheral resistance, $\frac{\text{mean B.P.}}{\text{C.O.}}$, is plotted (ordinate) for both acute intravenous (shaded area) and chronic oral treatment. The peripheral resistance tends to rise on prolonged treatment and to fall in the 1 case (M. Po.) in which treatment was withheld. Abscissa, days of treatment.

under therapy with similar findings each time (table 1, fig. 2).

Changes in mean circulation time could be compared in acute studies, but the difference in injection sites in the acute and chronic studies makes comparison questionable. Initial mean circulation times varied from 18 to 38 sec. After treatment with pentolinium bitartrate, the mean circulation time was increased in all but 1 patient, H.v A., and ranged from 21 to 40 sec. (table 1).

Pulmonary blood volumes were compared only in the acute experiments. Initial volumes varied from 1,365 to 2,795 ml. Reduction in blood pressure with pentolinium resulted in a reduction of pulmonary volume from 188 to 750 ml., which gives a percentage reduction of 9.0 to 38 per cent. The average reduction was 21.7 per cent (table 1).

In studies of total blood volume, no consistent or significant variation was noted under conditions of acute or continued pentolinium treatment.

The patient studied after discontinuing long-term therapy had a rise of 17 per cent in mean blood pressure. This was accompanied by a 4 per cent rise in cardiac index. There was a 1 per cent increase in stroke volume. There was a 15 per cent decrease in peripheral resistance as the blood pressure rose.

Discussion

The reductions in cardiac output and stroke volume noted in the sitting position after acute or chronic ganglionic blockade confirm the clinical impression of increased fatigue and weakness associated with this form of blood pressure depression. Failure of cardiac output to improve after long intervals of treatment is also confirmed by clinical experience; the patient who had been under treatment for 14 months noted improved strength when the drug was discontinued and the cardiac output and blood pressure rose. Despite these observations, we believe that pentolinium and other ganglionic-blocking agents perform a useful role in severe hypertension, both by reducing the arterial lesions that may follow sustained arterial hypertension but also by their effects on the heart, which undergoes a great reduction in work load, and on the lungs, which lose blood volume to the systemic circulation, as is shown by the regular reduction in pulmonary blood volume noted in these studies. A shift of 300 ml. of blood from lung to periphery could be very advantageous if pulmonary edema were incipient. Werko[9] also noted reductions in pulmonary blood volume in the recumbent position after ganglionic blockade. We are unable to explain the contrary observations of Gilmore and associates,[10] although they used a different method of calculating pulmonary blood volume.

The reduction in cardiac output *in the seated posture* appears to account entirely for the decline in blood pressure that is seen acutely or chronically. As stated previously, there are no comparable studies on the effects of chronic administration of ganglionic-blocking agents on cardiac output, and only a few observations of the acute effects of these agents in the orthostatic position. These latter are difficult to compare with our own observations. The studies of Gilmore and associates[10] in 4 patients using the direct Fick procedure showed "no accentuation of the usual reduction in cardiac output after tilting when the patient had been given C-6." Hickam and Pryor,[11] studying the cardiac output of 12 patients with postural hypotensive disease, recorded a reduction in output when they were tilted to 60°, which was usually no greater than that observed in the normal subject. When a large amount of albumin in saline solution was infused, the cardiac output increased and the blood pressure in some cases was maintained after tilting. This suggested "that these large output falls resulted from an inadequate venous return to the heart." It is to be noted that these 2 studies quoted are not strictly comparable to our own, since the patients were not studied in the sitting or tilted position both before and after ablation of neurogenic tone.

In the present study it is difficult to escape the conclusion that ganglionic blockade did not reduce arteriolar tone but acted upon the cardiac output through a reduction in venous return to the heart, as suggested for some of Hickam's cases. This theory would best explain the observations of Restall and Smirk[12] that immersion in water exactly cancels the effect of ganglionic blockade. The increase in tissue pressure so produced would hardly be of sufficient magnitude to reduce the lumen of arterioles, which normally maintain pressures greatly in excess of the pressure in the water bath, but such external pressure would be expected to correct exactly that decrement in peripheral venous pressure gradient brought about by the imposition of the force of gravity, and thus to "set" venous return, blood flow, and cardiac output at a new level. The decline of pulmonary blood volume noted in this study and in that of Werko and associates[9] can be explained on the basis of a peripheral shift of blood as a result of a new balance between pulmonary and peripheral arterial blood pressures.

If this conception of a *dynamic* change in venous flow rather than a *static* one can be accepted, other physiologic phenomena can be more easily explained. The normal reduction in cardiac output on standing may be explained as a failure of peripheral venoconstrictors to overcome the increased gravitational load. This change is nearly instantaneous and can be accomplished with minimal peripheral pooling or decrease in central venous pressure. Ganglionic blockade only serves to accentuate this normal tendency. Idiopathic or postsympathec-

tomy postural hypotension would lower blood pressure by a decrease in cardiac output mediated through a failure of normal peripheral venoconstriction as postulated by Hickam and Pryor.[11]

Although the studies reported here do not necessarily apply to the effect of ganglionic-blocking agents on the circulation in the *recumbent patient*, the importance of this subject in assessing "neurogenic" and "humoral" factors in hypertension[13, 14] justifies an attempt to extend the present theory to the action of these agents in the resting recumbent subject. As reviewed by Doyle and Smirk,[14] observations on cardiac output in the recumbent subject are in conflict, but a number of authors did not observe a change in the calculated peripheral arteriolar resistance when the drug was given intravenously to the recumbent hypertensive patient not in cardiac failure.[16-20] Crosley and co-workers[20] demonstrated a consistent decrease in cardiac output and right atrial pressure with no change or an increase in total peripheral resistance when pentolinium was given intravenously to the *recumbent* hypertensive subject. Their experiments would conform with the observation that, except for the hands and feet, no vascular bed in the hypertensive subject can be demonstrated to have an increased blood flow after ganglionic blockade,[21-23] and while vascular resistance falls in some of these areas, this occurs equally and *pari passu* with the blood pressure as if the vasodilatation were compensatory to the blood pressure fall rather than the primary factor in causing the reduction in blood pressure.

If we accept the fact that blood pressure reduction, even in recumbency, reflects chiefly a decreased cardiac output, it should be expected that decreased peripheral venous pressures and increased venous pooling should follow ganglionic blockade. Reductions in pressure in an isolated peripheral venous segment have been noted by Duggan, Love, and Lyons,[24] and, even in recumbency, Restall and Smirk[12] have shown that the blood pressure may be partially elevated by immersion in a water bath.[12] While venous pooling has not been demonstrated in the extremities, a considerable sequestration of blood in the liver has been noted by Bradley[25] after hexamethonium. These observations suggest that the major site of action of ganglionic blockade is on venoconstrictor tone, perhaps by reducing the peripheral-to-central venous pressure gradient and thus causing a decrease in cardiac output and systemic blood pressure. This gradient, which maintains venous return to the heart, is reduced still further in the orthostatic position, and is improved by returning to the recumbent posture, by infusion of norepinephrine or angiotonin, which actively constricts peripheral veins, or by increasing tissue pressure with steroids or salt infusions; all procedures that have been claimed to introduce a "humoral factor" into the maintenance of the blood pressure.[13, 14] If neurogenic tone is considered to include particularly peripheral veins and venules, then we should agree with Doyle and Smirk[14] that the over-all blood pressure response to ganglionic blockade is a measure of pre-existing neurogenic tone. Since "neurogenic tone" is usually considered to apply chiefly to the arterioles, which regulate peripheral resistance, we wish to emphasize that ganglionic-blocking agents may also affect blood pressure simply by altering neurogenic venous tone, and thus reduce blood pressure by reducing cardiac output. Such seems to be the mechanism of action in the patient with orthostatic hypotension induced by these agents.

Summary

A method is presented for determining cardiac output with radioactive iodinated serum albumin that permits multiple serial determinations and involves relatively simple apparatus. The intravenous injection of depressor doses of pentolinium bitartrate to hypertensive patients in the sitting position resulted in a decline in cardiac output and no change in total peripheral resistance. Blood was shifted from the pulmonary to the peripheral circulation. Continued effective oral treatment with this agent over a period of 6 to 128 days did not result in any long-term decline in peripheral resistance, the cardiac output in the sitting position remaining depressed over this time interval. When ganglionic blocking agents lower blood pressure in hypertension, they do so primarily

b· reducing venomotor tone, decreasing venous r turn, and lowering cardiac output. Their ef- f t on neurogenic arteriolar tone is minor.

Acknowledgment

The authors wish to express their appreciation t Dr. Alberto Agrest, University of Buenos Aires, A gentina, for his assistance, while a research f low in the Hypertension Unit, in setting up the p ocedure for cardiac output.

Summario in Interlingua

Es presentate un methodo pro determinar le r ndimento cardiac per medio del etiquettage d albumina seral con iodo radioactive. Le methodo permitte determinationes in serie e require un relativemente simple apparatura.

Le injection intravenose de doses depressori de bitartrato de pentolinium in patientes hypertensive in position sedente resultava in un declino del rendimento cardiac e in nulle alteration del total resistentia peripheric. Sanguine esseva transferite ab le circulation pulmonar verso le circulation peripheric. Le continue efficace tractamento oral con iste agente durante periodos de inter 6 e 128 dies non resultava in un declino tardive del resistentia peripheric, durante que le rendimento cardiac in position sedente remaneva deprimite. Quando agentes de blocage ganglionic reduce le pression sanguinee in hypertension, illos effectua iste resultato primarimente per reducer le tono venomotori, per reducer le retorno venose, e per reducer le rendimento cardiac. Lor effecto super le neurogene tono arteriolar es minime.

REFERENCES

1 Stewart, G. N.: Research on the circulation time and on the influences which affect it. IV. The output of the heart. J. Physiol. **22:** 159, 1897.

2 Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Simultaneous determination of the pulmonary and systemic circulation times in man and of a figure related to the cardiac output. Am. J. Physiol. **84:** 338, 1928.

3 —, —, —, and —: Simultaneous determination of the greater and lesser circulation times, of the mean velocity of blood flow through the heart and lungs, of the cardiac output and an approximation of the amount of blood actively circulating in the heart and lungs. Am. J. Physiol. **85:** 377, 1928.

4 —, —, —, and —: Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Am. J. Physiol. **99:** 534, 1931–1932.

5 Moore, J. W., Kinsman, J. M., Hamilton, W. F., and Spurling, R. G.: Studies on the circulation. II. Cardiac output determinations; comparison of the injection method with the direct Fick procedure. Am. J. Physiol. **89:** 331, 1929.

6 MacIntyre, W. J., Pritchard, W. H., Eckstein, R. W., and Friedell, H. L.: The determination of cardiac output by a continuous recording system utilizing iodinated $I^{(131)}$ human serum albumin. I. Animal studies. Circulation **4:** 552, 1951.

7 McMichael, J., and Sharpey-Schafer, E. P.: Cardiac output in man by a direct Fick method. Effects of posture, venous pressure change, atropine, and adrenaline. Brit. Heart J. **6:** 33, 1944.

8 Doyle, J. T., Wilson, J. S., Lepine, C., and Warren, J. V.: An evaluation of the measurement of the cardiac output and of the so-called pulmonary blood volume by the dye-dilution method. J. Lab. & Clin. Med. **41:** 29, 1953.

9 Werko, L., Frisk, A. R., Wade, G., and Eliasch, H.: Effect of hexamethonium bromide in arterial hypertension. Lancet **2:** 470, 1951.

10 Gilmore, H. R., Kopelman, H., McMichael, J., and Milne, I. G.: The effect of hexamethonium bromide on the cardiac output and pulmonary circulation. Lancet **2:** 898, 1952.

11 Hickam, J. B., and Pryor, W. W.: Cardiac output in postural hypotension. J. Clin. Invest. **30:** 401, 1951.

12 Restall, P. A., and Smirk, F. H.: Regulation of blood pressure levels by hexamethonium bromide and mechanical devices. Brit. Heart J. **14:** 1, 1952.

13 Ferris, E. B., Reiser, M. F., Stead, W. W., and Brust, A. A.: Clinical and physiological observations of the interrelated mechanisms of arterial hypertension. Tr. A. Am. Physicians **61:** 97, 1948.

14 Doyle, A. E., and Smirk, F. H.: The neurogenic component in hypertension. Circulation **12:** 543, 1955.

15 Freis, E. D., Rose., J. C., Partenope, E. A., Higgins, T. F., Kelley, R. T., Schnaper, H. W., and Johnson, R. L.: The hemodynamic effects of hypotensive drugs in man. III. Hexamethonium. J. Clin. Invest. **32:** 1285, 1953.

16 Werko, L., Frisk, A. R., Wade, G., and Eliasch, H.: Effect of hexamethonium bromide in arterial hypertension. Lancet **2:** 470, 1951.

17 Lynn, R. B., Sancetta, S. M., and Simeone, F. A.: A new ganglionic blocking agent. Angiology **3:** 241, 1952.

18 Mottu, T.: Artificial reduction of the heart effort. The effect of the association of hexamethonium

bromide and sodium amytal. Am. Heart J. **47:** 270, 1954.

[19] GROB, D., SCARBOROUGH, W. R., KALTUS, A. A. JR., AND LANGFORD, H. G.: Further observations on the effects of autonomic blocking agents in patients with hypertension. II. Hemodynamic, ballistocardiographic and electrocardiographic effect of hexamethonium and pentamethonium. Circulation **8:** 352, 1953.

[20] CROSLEY, A. P. JR., ROWE, G. G., BROWN, J. F., TUCHMAN, H., HUSTON, J. H., AND CRUMPTON, C. W.: The acute and chronic effects of Pentolinium Tartrate on water and electrolyte excretion in hypertensive patients. Circulation **12:** 690, 1955.

[21] FORD, R. V., MOYER, J. H., AND SPURR, C. L.: Hexamethonium in the chronic treatment of hypertension—its effect on renal hemodynamics and on the excretion of water and electrolytes. J. Clin. Invest. **32:** 1133, 1953.

[22] CRUMPTON, C. W., ROWE, G. G., CAPPS, R. C., WHITMORE, J. J., AND MURPHY, Q. R.: The effect of hexamethonium upon cerebral blood flow and metabolism in patients with pre-malignant and malignant hypertension. Circulation **11:** 106, 1955.

[23] REYNOLDS, T. B., PATON, A., FREEMAN, N., HOWARD, F., AND SHERLOCK, S.: The effect of hexamethonium bromide on splanchnic blood flow, oxygen consumption and glucose output in man. J. Clin. Invest. **32:** 793, 1953.

[24] DUGGAN, J. J., LOVE, V. L., AND LYONS, R. H.: A study of reflex venomotor reactions in man. Circulation **7:** 869, 1953.

[25] COMINSKY, B., PREEDY, J. R. K., WHEELER, H. O., HAYS, R. M., AND BRADLEY, S. E.: "Splanchnic pooling" during the hypotensive action of hexamethonium bromide in the dog. Abstracted, J. Clin. Invest. **33:** 924, 1954.

McKusick, V. A.: Carcinoid Cardiovascular Disease. Bull. Johns Hopkins Hosp. **98:** 13 (Jan.), 1956.

Two patients are described in whom cardiovascular manifestations accompanied metastasizing carcinoid. In 1, a 53-year-old man, diarrhea, "asthma," flushing attacks, and congestive heart failure accompanied biopsy-proven hepatic metastases whose origin was not identified. In the second patient, a 68-year-old woman, autopsy revealed extensive scarring and deformity of the valves of the heart in the following order of descending severity: pulmonic, tricuspid, mitral, aortic. An unusual feature that was thought to account for involvement of the valves on the left side was patency of the foramen ovale and right-to-left shunt. The presence of the last was attested to by the cyanosis and polycythemia present in life. These circumstances are consonant with the theory that the endocardial changes are produced directly by noxious substance(s) elaborated by the tumor, secreted into the blood stream, and partially destroyed in the lungs. The necessity for the presence of liver metastases suggests that the liver likewise destroys the noxious material. Another circumstance of the second case is the presence of only insignificant liver metastases, but of a huge metastasis to the ovary (which has its venous drainage directly to the vena cava) supports the view that the liver ordinarily destroys the noxious material, in part at least. In general, the behavior observed is that of serotonin, and a direct influence in the production of valvular lesions is suggested. Histologically, there were, in addition to chronic inflammatory changes, lesions with the appearance of platelet thrombi. Observations on a number of circulating patients are not available; the thrombocytosis observed in animals with injection of serotonin and in man with carcinoid tumor may have been present.

McKUSICK

Isolated Pulmonic Valvular Regurgitation

By RALPH F. MORTON, M.D., AND THOMAS N. STERN, M.D.

An extremely rare case of isolated organic insufficiency of the pulmonic valve is reported along with clinical and hemodynamic data.

ISOLATED nonsurgical pulmonic valvular regurgitation has been reported only twice during life in man.[1, 2] In fact, it is unusual to make a diagnosis of organic pulmonic insufficiency from any cause with any degree of certainty during life.[3] The following case is presented as one of symptomatic heart disease in an adult secondary to pulmonic valvular regurgitation.

CASE REPORT

V. H., a 20-year-old Negro housewife, was apparently normal at birth except for small supernumerary digits on each of her 4 extremities. As a child she was able to keep up with other children until her early teens when she noted easy fatigability on moderate exertion and inability to run because of dyspnea and marked dizziness. At 15 years of age she had pleurisy and shortness of breath for about 2 months. When seen by a physician, she was told that she had "heart trouble probably from birth." Shortly thereafter she had severe tonsillitis, but no rheumatism, chorea, or other stigmata of rheumatic fever. Her first pregnancy at 15 years of age terminated spontaneously at 3 months. During her second pregnancy at 20, moderate exertional dyspnea was noted, but delivery of a normal male infant was tolerated without evidence of heart failure. The patient had her first complete physical examination 3 months after her second pregnancy, when she developed cough, fever, and pleurisy of the right chest. In addition to evidence of pneumonitis, she was noted to have a heart murmur. After the pneumonitis responded to antibiotics, the patient was referred to the Cardiovascular Clinic of the City of Memphis Hospitals because of her murmur, mild dyspnea on exertion, and dizziness on moderate exertion.

The patient was normally developed. There was no dyspnea, cyanosis, or clubbing of the fingers. The pulse was 72 and the blood pressure 110/70. There was slight decrease in breath sounds over the right lower chest, but the chest and lungs were otherwise normal. The cardiac apex was in the fourth intercostal space, just medial to the midclavicular line. A moderate systolic impulse was noted along the left sternal border, and a diastolic thrill was localized at the pulmonic area. The pulmonic and apical second sounds were split. A soft, grade 2, moderately high pitched, holosystolic murmur was heard at the base of the heart, but was maximal at the pulmonic area. An early, rough, loud, decrescendo diastolic murmur was heard best at the second and third left intercostal spaces but also radiated along the left sternal border and to the midprecordium. The peripheral pulses were normal.

An electrocardiogram (fig. 1) revealed right bundle-branch block. The phonocardiogram (fig. 2) confirmed the murmurs previously described. The chest x-ray showed no increase in heart size, but prominence of the pulmonary artery was noted. Marked pulsations of the right ventricle and primary branches of the pulmonary artery were demonstrated on fluoroscopy and roentgenkymography (fig. 3). Pulsations of the pulmonary artery were much more prominent than those of the aorta.

Diagnoses considered prior to cardiac catheterization were atrial or ventricular septal defect with pulmonic insufficiency and patent ductus arteriosus.

Cardiac catheterization was performed on February 1, 1956. The catheter was introduced through a left antecubital vein, took the normal course through the pulmonary artery, and was wedged without difficulty. Marked whipping of the catheter was noted in the main pulmonary artery. Catheterization findings are summarized in table 1.

Right atrial mean pressure was within normal limits. Right ventricular and pulmonary artery systolic pressures were normal and essentially the same. The pulmonary arterial diastolic pressure was low and not significantly different from the right ventricular end-diastolic pressure. There was an abrupt steep slope of the catacrotic limb of the pulmonary pressure curve (fig. 4). This tracing was reproducible and, we believe, not an artifact. Oxygen saturations, oxygen consumption, cardiac output, cardiac index, pulmonary arterial flow, and pulmonary and peripheral resistances were all normal at rest.

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Dr. Morton is a Trainee of the National Heart Institute (1955–1956).

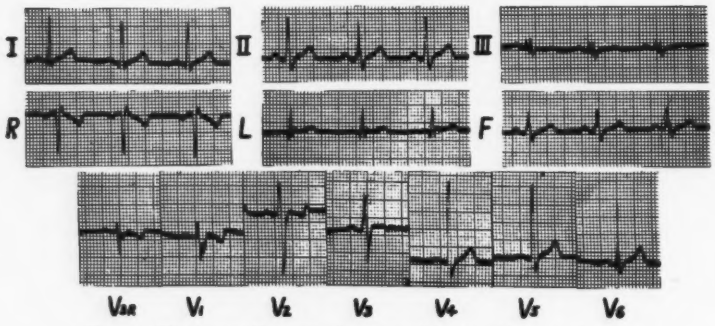

FIG. 1. Electrocardiogram showing right bundle-branch block.

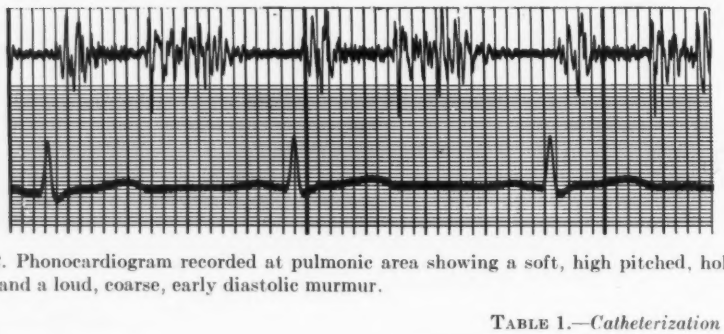

FIG. 2. Phonocardiogram recorded at pulmonic area showing a soft, high pitched, holosystolic murmur and a loud, coarse, early diastolic murmur.

TABLE 1.—*Catheterization Data*

Location	Oxygen content (vol. %)*	Pressures (mm. Hg)†
Superior vena cava	9.9	—
Right atrium	9.9	Mean 3.2
Right ventricle	10.1	22/3
Main pulmonary artery	9.9	21/2 Mean 8.9
Right pulmonary artery (distal)	10.3	17/2 Mean 7
Pulmonary wedge	—	Mean 4.2
Brachial artery	14.0 (99.2% sat.)	104/68 Mean 80

A-V oxygen difference 3.9 vol. per cent.
Oxygen consumption 245 ml./min.‡
Systemic flow 6.1 L./min.
Cardiac index 3.4 L./min./M.²
Pulmonary artery flow 6.1 L./min.
Pulmonary arteriolar resistance 51 dynes sec. cm.$^{-5}$
Total pulmonary resistance 105 dynes sec. cm.$^{-5}$
Total peripheral resistance 1048 dynes sec. cm.$^{-5}$

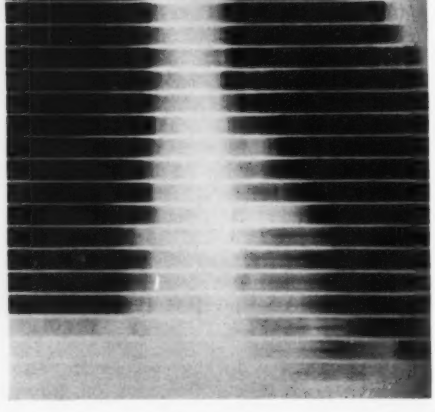

FIG. 3. Roentgenkymogram showing marked pulsations of the main pulmonary artery that are greater than those of the aorta.

* Determined according to the technic of Van Slyke and Neill.

† Recorded with a Statham strain-gage manometer and Sanborn recorder.

‡ Measured with a Collins Respirometer.

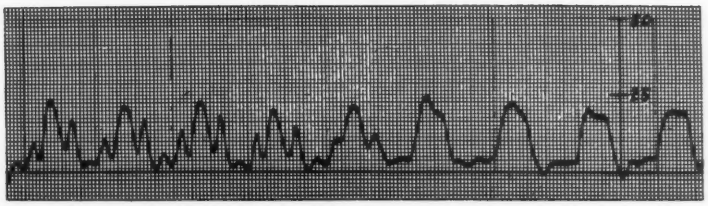

FIG. 4. Pressure curves recorded as the catheter was withdrawn from main pulmonary artery into the right ventricle.

DISCUSSION

Whereas isolated valvular pulmonic stenosis has in recent years been recognized to be a relatively common congenital anomaly,[4] other organic pulmonary valve lesions, either congenital or acquired, are very rare.[5] Organic pulmonary insufficiency due to congenital absence of valve cusps[6] and due to an abnormal number of cusps, 2, 4, or 5,[7] has been reported from autopsy material. Recently, pulmonary insufficiency was conclusively diagnosed during life in a patient with pulmonic stenosis and an interventricular septal defect.[3] Rare causes for acquired pulmonic regurgitation are rheumatic fever, syphilis, acute bacterial endocarditis,[8] and trauma to the chest.[9]

Functional pulmonic insufficiency due to any condition resulting in dilatation of the pulmonary artery with stretching of the valve ring is generally considered to be quite common; however, statistics regarding its frequency are varied and unreliable.[10] This is, of course, never an isolated abnormality.

The diagnosis of pulmonic regurgitation has in the past been based on the presence of a soft blowing diastolic murmur heard best in the second or third left intercostal space, and has required the absence of peripheral signs of aortic regurgitation.[11, 12] It is now generally recognized that this in itself is not adequate evidence for a diagnosis of pulmonic insufficiency.[3] At the present time one is no longer handicapped by the lack of objective methods for making a diagnosis of pulmonic insufficiency during life. Flouroscopy, by demonstrating a collapsing pulse or hilar dance of the pulmonary vessels, is a valuable aid.[13, 14] An electrokymographic tracing of the pulmonary knob reveals high pulsations that are larger than those of the aorta. In addition, the pulsations have a rapid rise and collapse.[15] Cardiac catheterization probably provides the best evidence for the presence of pulmonic regurgitation. A widened pulmonary artery pulse pressure may be revealed.[15] However, as pointed out by Kohout and Katz,[3] "More important, in that it establishes the diagnosis of pulmonic insufficiency, is the abrupt slope of the catacrotism to a value practically identical with that in the right ventricle, and the remainder of the diastolic portion of the pulmonary artery pressure curve is horizontal."

Very few instances of pulmonic insufficiency have been conclusively diagnosed during life. Pulmonic insufficiency associated with other cardiac abnormalities has been diagnosed by means of cardiac catheterization[3, 4, 16, 17]; however, to our knowledge, only 2 cases of isolated nonsurgical pulmonic valvular regurgitation diagnosed ante mortem have been reported.[1, 2]

In our case, the murmur and its phonocardiographic picture, the fluoroscopic findings, and the pulmonary artery pressure curve are quite compatible with a diagnosis of pulmonary valvular insufficiency without associated defect. It is of interest to note that the electrocardiogram showed evidence of right bundle-branch block. Though this pattern is not specific for pulmonic regurgitation, it is the expected finding according to the concept of Cabrera[18] that diastolic overloading of the right ventricle causes right bundle-branch block. It cannot be stated with certainty whether this is a congenital or an acquired defect of the valve, since the patient was not examined prior to 15 years of age.

There is no guide to the prognosis of this apparently pure pulmonic valve lesion, inas-

much as the only other reported cases were those of a 7-year-old child who was asymptomatic[1] and a 44-year-old woman who developed congestive heart failure and died of unknown cause.[2] The latter case, however, was complicated by the presence of diffuse pulmonary fibrosis secondary to tuberculosis. We believe our case to be the only reported instance of uncomplicated, isolated pulmonic valvular regurgitation with symptoms. Even experimentally produced pulmonic regurgitation[19] and that resulting from surgical correction of pulmonic stenosis[4] after short-term follow-up failed to produce right heart failure. We will, therefore, watch our patient's subsequent course with great interest.

Summary

A case of isolated nonsurgical pulmonic regurgitation, believed to be the third instance diagnosed during life, is presented. Diagnosis was suggested by physical examination, phonocardiography, and fluoroscopy and was definitely established by cardiac catheterization.

Summario in Interlingua

Es presentate un caso de isolate non-chirurgic regurgitation pulmonic. Secundo le informationes del autores, isto es le tertie tal caso con establimento del diagnose durante le vita del patiente. Le diagnose esseva suggerite per le examine physic e per phonocardiographia e fluoroscopia. Illo esseva definitivemente establite per catheterisation cardiac.

REFERENCES

[1] Kjellberg, S., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease. Chicago, The Year Book Publishers, Inc., 1955.

[2] Ford, A. B., Hellerstein, H. K., Wood, C., and Kelly, A. B.: Isolated congenital bicuspid pulmonary valve. Am. J. Med. **20:** 474, 1956.

[3] Kohout, F. W., and Katz, L. N.: Pulmonic valvular regurgitation. Am. Heart J. **49:** 637, 1955.

[4] Blount, S. G., Jr., McCord, M. C., Mueller, H., and Swan, H.: Isolated valvular pulmonic stenosis, Circulation **10:** 161, 1954.

[5] White, P. D.: Heart Disease. Ed. 3. New York, The Macmillan Company, 1951.

[6] Lavenne, F., Tyberghein, J., Brasseur, L., and Meerseeman, F.: Complexe d'Eisenmenger avec insuffisance pulmonaire par absence de valvules. Acta cardiol. **9:** 249, 1954.

[7] Kissin, M.: Pulmonary insufficiency with a supernumerary cusp in the pulmonary valve. Am. Heart J. **12:** 206, 1936.

[8] McGuire, J., and McNamara, R. J.: Organic and relative insufficiency of the pulmonary valve. Am. Heart J. **14:** 562, 1937.

[9] Stoldt, Deutsche med. Ztschr. **31:** 9, 1902; *In* Vaquez, H.: Maladies de Coeur. Paris, J. B. Bailliere et Fils, 1921.

[10] Friedberg, C. K.: Diseases of the Heart. Philadelphia, W. B. Saunders Co., 1949.

[11] Schwartz, S. P.: The radiographic signs of pulmonic insufficiency. Am. Heart J. **2:** 407, 1927.

[12] Bourne, G.: Pulmonary regurgitation. Lancet **2:** 1427, 1937.

[13] Dressler, W.: Clinical Cardiology. New York, Paul B. Hoeber, Inc., 1942.

[14] Schwedel, J. B.: Annals of Roentgenology, Vol. 18. Clinical Roentgenology of the Heart. New York, Paul B. Hoeber, Inc., 1950.

[15] Luisada, A. A.: The Heart Beat. New York, Paul B. Hoeber, Inc. 1953.

[16] Joly, P. F., Charlotte, J., and Sicot, J. R.: Les communications interventriculaires (diagnostic par catheterisme). Etude clinique et physiologique. Arch. mal. coeur **44:** 602, 1951.

[17] Giraud, G., Latour, H., Levy, A., Puech, P., and Mimran, R.: Les courbes de pression pulmonaire et ventriculaire driote dans l'insuffisance sigmoidienne pulmonaire congenitale. Montpellier méd. **39–40:** 472, 1951.

[18] Cabrera, C. E., and Monroy, J. R.: Systolic and diastolic loading of the heart. II. Electrocardiographic data. Am. Heart J. **43:** 669, 1952.

[19] Fowler, N. O., Mannix, E. P., and Noble, W.: Some effects of partial pulmonary valvectomy. Circulation Research **4:** 8, 1956.

Intra-Atrial Block

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Attention is drawn to differences of opinion regarding the upper normal limit of P-wave duration and the definition of intra-atrial block. There seems to be good reason for accepting 0.11 sec. as the upper limit of normal and a P-wave duration of 0.12 sec. or more as indicative of intra-atrial block. By this criterion 4,500 consecutive electrocardiograms taken in a general hospital were examined and the findings are reported.

ALTHOUGH proposed definitions of intra-atrial block vary, a number of authorities consider that the criterion for diagnosis is a P wave measuring 0.12 sec. or longer.[1] It is our impression that most electrocardiographers pay little attention to the duration of the P wave in routine interpretation and consequently have little conception of the relative frequency of intra-atrial block. Systematic scrutiny of the P waves in the course of interpreting records in a general hospital has revealed that intra-atrial block, as defined above, is a common finding, accounting for nearly one third of all types of blocks encountered.

The purpose of this communication is to draw attention to the high incidence of intra-atrial block and to discuss criteria for its diagnosis.

MATERIAL AND METHODS

All electrocardiograms were taken with Sanborn or Cambridge direct-writing instruments. In the course of daily interpretation of inpatient and outpatient records in a general hospital, the duration of P waves was routinely observed in 4,500 tracings, almost all of which were 12-lead records. The sole criterion for recording intra-atrial block was the finding *in any lead* of P waves measuring 0.12 sec. or more. When notching with peak interval of more than 0.04 sec. was present it was noted in addition; but where such notching occurred in the absence of a duration of 0.12 sec., intra-atrial block was not recorded.

The difficulties in exact measurement of P-wave duration are well appreciated. We have accepted P-wave prolongation only in those tracings in which the beginning and end of the P waves were clearly distinguishable in at least 1 lead. Where definition was not sufficiently clear, because, for example, of alternating current interference or muscle tremors, even though it seemed probable that the P waves spanned 0.12 sec., the diagnosis of intra-atrial block was not recorded. Other sources of error occur when the preceding U wave merges with the P wave making the true onset of atrial activity uncertain or when the P wave merges imperceptibly at its end with the T_P wave. When for either of these reasons the beginning or end of the P wave could not be determined with reasonable accuracy, intra-atrial block was not recorded even if it were suspected.

In the great majority of tracings, P-wave prolongation was noted and measured in 1 of the limb leads. But there would seem to be no good reason for selecting any particular lead or set of leads as the best arbiter of the duration of atrial activation and we have followed the logical dictum of Ashman and Hull[2] that "the P wave must be measured in the lead where it is widest." We have also taken clarity of inscription into account and if P waves were unusually clearly written in precordial leads, 1 of these was used for more exact measurement. The actual number of times that each lead was used for the recorded measurement was as follows: lead I, 8; lead II, 124; lead III, 25; aV_R, 22; aV_L, 2; aV_F, 17; V_1, 1; V_3, 3; V_5, 1.

RESULTS

Among 4,500 electrocardiograms consecutively interpreted by one of us, 203 (4.5 per cent) were found to contain P waves of at least 0.12 sec. duration. These 203 tracings were derived from 150 patients. The incidence of P-wave durations is given in table 1 together with the incidence of significant notching found for each duration-group. Samples of various types of P waves classified as intra-atrial block are presented in figure 1.

Among these 4,500 tracings, there were 221 examples of atrioventricular block and 239 of

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intraventricular block. The incidence of the various blocks encountered is detailed in table 2. It is clear that intra-atrial block, by the definition here employed, is almost as common as either atrioventricular or intraventricular block.

TABLE 1.—*Incidence of Various Durations of P Waves and the Incidence of Notching in Each Group*

Duration (sec.)	Number	Notching
0.12	116	9
0.13	50	8
0.14	21	3
0.15	8	2
0.16	7	—
0.17	1	—
	203	22

DISCUSSION

Definition of Intra-Atrial Block

Katz[3] reported "300" instances of intra-atrial block among "about" 47,000 records

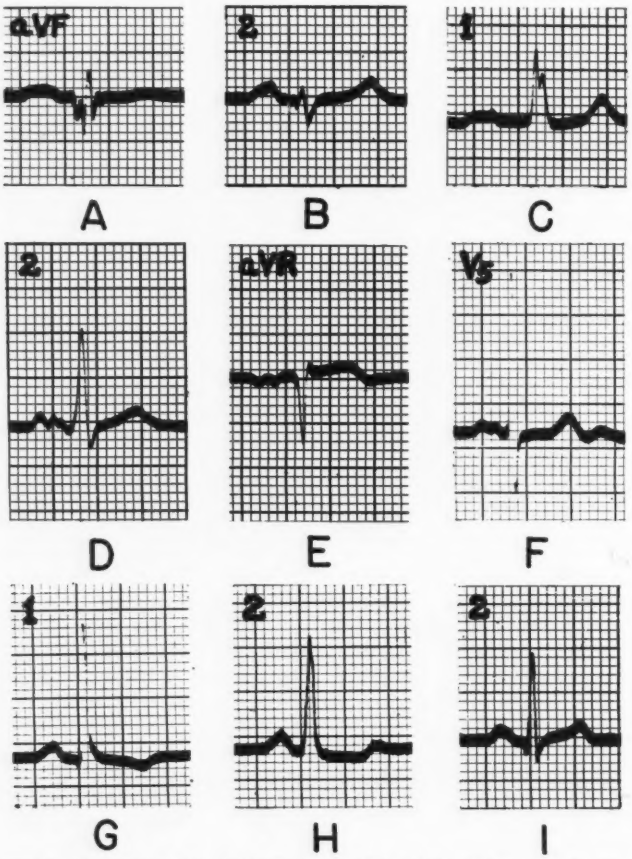

FIG. 1. Examples of P waves that indicate intra-atrial block. Those in the top row show gross prolongation (0.15 to 0.16 sec.) without true notching. Those in the middle row show gross notching with peak interval of 0.04 sec. or more. Those in the bottom row might well be passed as normal in routine interpretation, but they measure 0.12 sec. and, we believe, probably indicate atrial abnormality.

A and *B* are from aged patients with arteriosclerosis; *C*, *F*, and *I* are from patients with rheumatic heart disease; *D* is from a patient with severe hypertension shortly before the onset of atrial fibrillation; *E* is from another patient with severe hypertension who had previously had atrial fibrillation; *G* and *H* are also from hypertensive patients.

TABLE 2.—*Incidence of the Various Heart Blocks in 4,500 Tracings*

	Number	Percentage
S-A block	17	3
Intra-atrial block	203	30
A-V block	221	33
first degree*	195	29.1
second degree†	18	2.7
complete‡	8	1.2
Intraventricular block	239	36
complete LBBB	77	11.5
complete RBBB	70	10.4
others§	92	13.7
	680	

* Excluding isolated finding with atrial premature beats or after interpolated ventricular premature beats.

† Excluding the block associated with atrial flutter and tachycardia.

‡ Excluding those instances associated with atrial fibrillation.

§ Including incomplete BBB, peri-infarction and other atypical intraventricular blocks.

(about 0.64 per cent). This represents an incidence about one seventh of ours. In Katz' series, however, it is not certain what criterion was used for the diagnosis, because he defined intra-atrial block differently at 2 places in his text. On page 772 he required a P wave "prolonged to or beyond 0.12 sec., especially if notched and large," whereas on page 142 he stated that P waves "over 0.12 sec. are abnormal, and those between 0.10 and 0.12 sec. should be viewed with suspicion." If in our series only those P waves measuring 0.13 sec. or more are accepted as evidence of intra-atrial block, we are left with a total of 87 records giving an incidence of 1.9 per cent; this is still 3 times the approximate incidence recorded by Katz. It is of interest that in the revised volume by Katz and Pick,[4] in which the table of incidence of the various arrhythmias is now based on about 100,000 records, intra-atrial block has been omitted from the table.

Emphasis is often placed on notching as well as prolongation of P waves. Bellet[5] gave as his requirements for intra-atrial block a P wave of more than 0.12 sec. duration that is also full and notched. We do not believe that either notching or height is necessary to the diagnosis of intra-atrial block. The records A, B, and C in figure 1 all show gross prolongation and therefore, we believe, give unequivocal evidence of intra-atrial block. None of the 3 shows true notching and A shows little amplitude. All 3 were from grossly diseased hearts.

Normal Upper Limit of P-Wave Duration

There is no uniformity of opinion concerning the normal upper limit of P-wave duration. Many authorities regard 0.10 sec. as the normal maximum, while, at the other extreme, some consider that a duration in excess of 0.12 sec. is sometimes a normal finding.

Evidence and Opinion Placing 0.10 sec. as the Upper Limit. White[6] and Luisada,[7] stated that the upper limit of normal was 0.10 sec. The Criteria Committee of the New York Heart Association[1] defined a "broad" P wave as one that exceeded 0.10 sec. in 1 of the standard leads. Sorsky and Wood[8] found a maximum P-wave width of 0.10 sec. in the limb leads of 114 normals, but the majority of their subjects were under the age of 16 years. Among 100 normal subjects Thomas and Dejong[9] found no P waves of longer duration than 0.10 sec. Recently Gibert-Queralto and associates[10] considered P waves in excess of 0.10 sec. to be abnormal.

Evidence and Opinion Placing 0.11 sec. as the Upper Limit. Ashman and Hull,[2] Katz,[3] Goldberger,[11] Scherf and Boyd,[12] Burch and Winsor[13] all stated that 0.11 sec. was the maximum normal duration. Among 100 normals Ashman and Hull found only 1 record in which P waves exceeded 0.10 sec. In a study of mitral valve disease and its influence on the electrocardiogram, White and his colleagues[14] concluded that P waves of over 0.11 sec. duration in any lead should be considered abnormal. Stewart and Manning[15] came to a similar conclusion after analyzing the records of 500 healthy airmen between the ages of 18 and 32; there were 37 examples of P waves longer than 0.10 in lead II, with fewer instances in the other standard leads. From their analysis they concluded that 0.12 sec. represented a significant prolongation.

Evidence and Opinion Placing the Upper Limit Above 0.11 sec. Among the champions of

longer normals, Lepeschkin[16] stated that the upper limit was 0.12 sec. Shipley and Hallaran[17] examined the records of 200 normal adults and found a P-wave duration of 0.11 sec. in 13, and 0.12 sec. in 3 (1.5 per cent). Graybiel and his co-workers[18] found a similar incidence of 0.12 sec. P waves when they analyzed the tracings of 1,000 normal airmen between the ages of 20 and 30; 15 (1.5 per cent) had P waves in lead II measuring 0.12 sec., with smaller incidences in the other standard leads. It has been implied in a later work by Graybiel and co-authors[19] that the normal P wave may rarely exceed 0.12 sec. in duration.

Justification for Applying the Term Intra-Atrial Block to Prolonged P Waves

It is customary to apply the term intraventricular block to QRS complexes of 0.12 sec. or more (provided ectopic ventricular rhythms and pre-excitation have been excluded). The term is applied to widened complexes even when it is clear, or at least probable, that the widening is the result of ventricular enlargement rather than true block. By analogy, if one could establish an agreed critical limit for P-wave duration, it would be reasonable to apply the term intra-atrial block to all P waves exceeding this limit even when the presumable cause was atrial enlargement.

Justification for Adopting 0.11 sec. as the Upper Normal Limit of P-Wave Duration

From 2 points of view we believe that the figure 0.11 can be justified. It is obvious that for P-wave duration, as with all biologic values, no clear-cut dividing line can be drawn between normal and abnormal. Wherever the line is drawn there will be some normals on the "abnormal" side of it and some abnormals on the "normal" side. The best that one can hope to achieve is to determine the point at which overlap is minimal. It is customary to place the upper limit of normality at a point that will contain 98 per cent of the normal population.[20] To find this point one must obviously appeal to the largest available series of normals. The only 2 sizable series of normal adults in which we are given the number who had P waves of 0.11 and 0.12 sec. are those of Graybiel and associates[18] and of Shipley and Hallaran.[17] From these workers' figures, involving a total of 1,200 normal subjects, it would seem that 98 to 98.5 per cent of normal subjects have P waves that measure less than 0.12 sec. By this standard, therefore, the line between "normal" and "abnormal" may reasonably be drawn between 0.11 and 0.12 sec.

A second approach is to observe what company the P wave in question keeps. An analysis of the 150 patients, from whom the 203 tracings showing intra-atrial block were obtained, shows that their electrocardiograms contained the following concomitant abnormalities:

Left ventricular hypertrophy and strain	68
First degree A-V block	47
Myocardial infarction, previous or contemporary	38
ST-T abnormalities, nonspecific	27
Atrial fibrillation, previous or subsequent	18
Left bundle-branch block	6
Right bundle-branch block	6
Complete A-V block	6
Second degree A-V block	4
Right ventricular hypertrophy and strain	4
Other abnormalities (incomplete intraventricular block, previous atrial flutter, etc.)	10
	234

In other words, the 150 patients showing intra-atrial block amassed between them a total of 234 other electrocardiographic abnormalities. Of these 150 there were only 7 patients whose tracings showed no other definite abnormality. Of these 7, 2 had hypertension and 1 suffered from angina and had previously been in congestive failure. Thus there were only 4 of the 150 patients with prolonged P waves in whom there was no good reason to suspect cardiac abnormality. Two of these 4 had P waves measuring 0.12 and the other 2 measured 0.13 sec. From this analysis we venture to conclude that the great majority of P waves measuring 0.12 sec. are associated with cardiac abnormalities and probably reflect atrial involvement.

Known Causes of P-Wave Prolongation

A number of factors are known to be capable of lengthening the time of atrial activation. Digitalis, quinidine, and vagal stimulation all can increase the duration of the P wave.

Again, left atrial enlargement, as seen in mitral disease and in hypertension, produces lengthening of the P wave presumably mainly because of the additional time required for the impulse to reach the outposts of the enlarged atrium. Coronary sclerosis can also lead to P-wave prolongation; the best documented mechanism for this is impairment of blood flow through Condorelli's artery (left anterior atrial artery), which supplies Bachmann's bundle and other inter-atrial connections. Experimental occlusion of Condorelli's artery or clamping of Bachmann's bundle has been shown to produce intra-atrial block and even at times atrial dissociation.[21, 22]

In this connection it may be of interest to note the clinical associations in our series of prolonged P waves. Our figures are conservative because clinical information about many of the patients was incomplete as we are dependent to a large extent on data (often inadequate) supplied by private physicians at the time of referral for an electrocardiogram. Of the 150 patients, over half (79) were hypertensive, 56 had evidence of coronary disease, 11 had rheumatic, and 2 had syphilitic heart disease. At least 34 of the patients were taking digitalis and 6 were receiving quinidine.

Although Shipley and Hallaran[17] and Ashman and Hull[2] were unable to demonstrate any relationship between heart rate and duration of P waves, Lepeschkin[16] stated, on what he admitted might be unreliable evidence, that P-wave duration decreases with increasing heart rate; from his graph it appears that a P wave measuring 0.09 sec. at a rate of 55 may be expected to measure 0.07 sec. at a rate of 135. It has apparently been shown recently that *total* atrial activity (P plus T_P) varies inversely with atrial rate.[23] If further evaluation confirms that the duration of the P wave itself is related to rate, it will obviously be undesirable and inaccurate to abide by an arbitrary limit for P-wave duration that makes no allowance for the prevailing rate; further study may show, for instance, that 0.12 sec. is always an abnormal duration at a rate of 100 but is within normal range at half this rate.

Summary

In 4,500 consecutive electrocardiograms taken in a general hospital, P-wave duration was routinely noted. With a P-wave duration of 0.12 sec. or more as the criterion for diagnosing intra-atrial block, this diagnosis was recorded in 203 tracings, or 4.5 per cent. This incidence was almost as high as that of atrioventricular or intraventricular block in the same series. Only 22 of the 203 records showed significant notching of P waves (peak interval of 0.04 sec. or more). Criteria for the diagnosis of intra-atrial block are discussed and reasons for accepting 0.11 sec. as the upper normal limit of P-wave duration are given. Known causes of P-wave prolongation are briefly reviewed.

Summario in Interlingua

In 4500 electrocardiogrammas consecutive in un hospital general, le duration del unda P esseva notate routinarimente. Un duration del unda P de 0,12 secundas o plus esseva usate como criterio del diagnose de bloco intra-atrial. Super iste base, le diagnose de bloco intra-atrial esseva obtenite in 203 registrationes, i.e. in 4,5 pro cento del serie total. Iste incidentia esseva quasi tanto alte como le incidentia de bloco atrioventricular o intraventricular in le mesme serie. Solmente 22 del 203 registrationes monstrava significative grandos de indentation del undas P (intervallo del culmines amontante a 0,04 secundas o plus). Es discutite criterios pro le diagnose de bloco intra-atrial. Es explicate le rationes pro le acceptation de 0,11 secundas como limite superior del duration normal del unda P. Le recognoscite causas del prolongation del unda P es revidite brevemente.

REFERENCES

[1] Criteria Committee of New York Heart Association, Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. Ed. 5, N. Y. Heart Association Inc., New York, 1953.

[2] Ashman, R., and Hull, E.: Essentials of Electrocardiography. Ed. 2, New York, The Macmillan Co., 1945.

[3] Katz, L. N.: Electrocardiography. Philadelphia, Lea and Febiger, 1946.

[4] —, and Pick, A.: Clinical Electrocardiography. Part I. The Arrhythmias. Philadelphia, Lea and Febiger, 1956.

[5] BELLET, S.: Clinical Disorders of the Heart Beat. Philadelphia, Lea and Febiger, 1953.
[6] WHITE, P. D.: Heart Disease. Ed. 4, New York, The Macmillan Co., 1951.
[7] LUISADA, A. A.: Heart. Ed. 2., Baltimore, The Williams and Wilkins Co., 1954.
[8] SORSKY, E., AND WOOD, P.: The use of chest leads in clinical electrocardiography. Am. Heart J. **13:** 183, 1937.
[9] THOMAS, P., AND DEJONG, D.: The P wave in the electrocardiogram in the diagnosis of heart disease. Brit. Heart J. **16:** 241, 1954.
[10] GIBERT-QUERALTO, J., TORNER-SOLER, M., AND BALAGUER-VINTRO, I.: The electrocardiogram in mitral stenosis before and after commissurotomy. Am. Heart J. **49:** 548, 1955.
[11] GOLDBERGER, E.: Unipolar Lead Electrocardiography and Vectorcardiography. Ed. 3, Philadelphia, Lea and Febiger, 1953.
[12] SCHERF, D., AND BOYD, L. J.: Clinical Electrocardiography. Ed. 4, New York, Grune and Stratton, 1953.
[13] BURCH, G. E., AND WINSOR, T.: A Primer of Electrocardiography. Ed. 3, Philadelphia, Lea and Febiger, 1955.
[14] WHITE, B. V., PARKER, R. C., AND MASTER, A. M.: Disease of the mitral valve: its effect on the pattern of the electrocardiogram. Arch. Int. Med. **74:** 95, 1944.
[15] STEWART, C. B., AND MANNING, G. W.: A detailed analysis of the electrocardiograms of 500 R.C.A.F. aircrew. Am. Heart J. **27:** 502, 1944.
[16] LEPESCHKIN, E. E.: Modern Electrocardiography. Vol. I. The P-Q-R-S-T-U complex. Baltimore, The Williams and Wilkins Co., 1951.
[17] SHIPLEY, R. A., AND HALLARAN, W. R.: The four-lead electrocardiogram in 200 normal men and women. Am. Heart J. **11:** 325, 1936.
[18] GRAYBIEL, A., MCFARLAND, R. A., GATES, D. C., AND WEBSTER, F. A.: Analysis of the electrocardiograms obtained from 1000 young healthy aviators. Am. Heart J. **27:** 524, 1944.
[19] —, WHITE, P. D., WHEELER, L., AND WILLIAMS, C.: Electrocardiography in Practice. Ed. 3., Philadelphia, W. B. Saunders Co., 1952.
[20] SIMONSON, E.: Criteria of normality in clinical electrocardiography. Bull. Univ. Minn. Hosp. **23:** 371, 1952.
[21] CONDORELLI, L.: Experimentelle Untersuchungen uber die interaurikulare Reizleitung. Ztschr. ges. exper. Med. **68:** 516, 1929.
[22] SCHERF, D., AND SIEDEK, H.: Uber Block zwischen beiden Vorhofen. Ztschr. klin. Med. **127:** 77, 1934.
[23] KESSELMAN, R. H., BERKUN, M. A., DONOSO, E., AND GRISHMAN, A.: The duration of atrial electrical activity and its relationship to the atrial rate. Am. Heart J. **51:** 900, 1956.

If "idle star-gazers" had not watched long and carefully the motions of the heavenly bodies—our modern astronomy would have been impossible, and without our astronomy "our ships, our colonies, our seamen," all which makes modern life could not have existed. Ages of sedentary, quiet, thinking people were required before that noisy existence began, and without those pale preliminary students it never could have been brought into being. And nine-tenths of modern science is in this respect the same: it is the produce of men whom their contemporaries thought dreamers—who were laughed at for caring for what did not concern them—who, as the proverb went, "walked into a well from looking at the stars."—WALTER BAGEHOT, 1826–1877.

The Abnormally Situated Azygos Vein

X-Ray Demonstration of its Distention in Congestive Failure and in Various Positions

By ROBERT N. ARMEN, M.D., F.A.C.P., AND CHARLES S. MORROW, M.B., CH.B. (EDIN.)

The azygos vein may be abnormally situated due to anomalous embryologic development. Its abnormal location is infrequent, but radiologic recognition is much easier than that of the normal vein. This vein, normal or abnormal, becomes distended in conditions with an elevated venous pressure, systemic or portal. Changes in the size of the azygos vein on x-ray are noted to parallel fluctuations of venous pressure. We have demonstrated such changes in a patient with an abnormally situated vein during congestive failure, after recovery, and in various physical positions. X-ray demonstration of such changes can have significant diagnostic application.

THE recognition of the normal azygos vein in posteroanterior chest films is not easy, because its shadow merges and is often obscured by the prominent densities of the vertebral column and structures at the root of the lung. In 1918, Crane[1] first described the "inverted comma sign," but failed to associate it with the azygos vein. Years later, in 1931, Ottonello[2] recognized the inverted comma as the arch of the azygos vein and described it fully. Stauffer, Labree, and Adams[3] believed that the normally situated azygos vein can be recognized frequently in the right anterior oblique position and that the image of its arch is almost constant in anteroposterior planigrams of the chest at the level of the bifurcation of the trachea. In general, though, it is more often missed than recognized. However, the abnormally situated azygos vein, associated with an azygos lobe of the right lung, is more readily recognized on chest films because it is situated more laterally and because of the pleural "mesentery" of the vein, which divides the right upper lobe.[4] On posteroanterior chest films, this "mesentery," or the fissure of the vein, is seen as a curved hairline shadow, at the right apex, with its convexity outward and running obliquely from above the hilus toward the right shoulder.[5] At its upper end a small triangular fuzzy peak may be noted; at its lower end is a small pear-shaped or comma-shaped shadow which is thought to represent the arch of the vein projected "end-on."[5] The differentiation between the normally and the abnormally situated vein is not difficult. The aberrant vein always has pulmonary parenchyma on each side and is associated with the curved hairline, while the normal vein lies along the right border of the trachea or the right main bronchus completely within the mediastinum.

That distention of the superior and inferior venae cavae and their tributaries results from the increased venous pressure in congestive heart failure is well known. This distention is easily appreciated by the naked eye in the superficial veins of the neck and of the upper extremities. However, in the case of the azygos vein, which is a deep tributary of the superior vena cava, its distention can be recognized only by roentgenologic identification of the enlarged pear-shaped or circular shadow of the arch of the vein. Various authors have described changes in the size of the shadow of the azygos vein in relation to elevated venous pressure and congestive failure.[3, 6-8] Except for Joselevich and Mactas,[6] they have dealt with normally situated azygos veins. These 2 authors reported instances of distention of both the abnormal azygos and the normally situated azygos veins in cardiac failure. Recently, we have observed an aberrant azygos vein in a patient with cardiac failure. It is the purpose of this paper to present this case of pulmonary heart disease in congestive failure with chest films showing

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(1) marked distention of the abnormally situated azygos vein while the patient was in right-sided heart failure, (2) disappearance of the distention after recovery from heart failure, and (3) marked distention of the azygos vein with the well compensated patient in the Trendelenburg position.

Anatomy of the Normal and Aberrant Azygos Vein

The azygos vein[4, 5, 9, 10] originates below the diaphragm opposite the first or second lumbar vertebra, usually as the right ascending lumbar vein; occasionally it arises as a branch from the right renal vein or a branch from the inferior vena cava. It enters the thorax through the aortic hiatus in the diaphragm and proceeds along the right side of the vertebral column. At the level of the fourth thoracic vertebra it arches forward over the root of the lung and empties into the superior vena cava just outside the pericardium. It drains the venous blood principally from the chest wall through the intercostal and the hemiazygos veins. It also receives several esophageal, mediastinal, pericardial, and pleural veins. In obstruction of the inferior vena cava, the azygos vein is among the principal channels through which blood is returned to the heart. Through its connections with esophageal veins it also forms part of the collateral circulation of the portal system. Actually, in many cases of advanced portal hypertension, the azygos vein is distended to a large size.

The abnormally situated azygos vein owes its existence to an anomaly in its embryologic development. It is always associated with an azygos lobe of the right lung. The incidence of the latter is not high. Anson reports it as 0.5 per cent in his series.[10] At our hospital its incidence is about 0.15 per cent. In early fetal life the azygos vein runs over the apex of the right lung, but as the lung grows upwards, the vein is normally pulled down by the heart and it finally arches over the root of the lung. If this gliding movement is arrested, the venous loop of the azygos vein indents the lung and produces a deep cleft in the apex of the right upper lobe. As the lung grows farther upwards the vein becomes deeply imbedded in it, drawing down a double fold of both parietal and visceral pleurae. This is often referred to as the "mesentery of the vein" or the "fissure of the vein," and consists of 4 layers of pleura. It should be emphasized that the normally situated vein and its arch lie entirely outside the lung and within the mediastinum, whereas lung parenchyma lies on each side of the arch of the anomalous vein.

Case Report

The patient, a 60-year-old white male coal miner, was first admitted to this hospital in March 1954 for a minor surgical problem. He was found to have anthracosilicosis, emphysema, and chronic bronchitis. Although the electrocardiogram was considered to be probably abnormal, the evidence of heart disease was not conclusive and the patient was not in cardiac failure. The heart was of normal size on x-ray.

The second admission was from January 27 to February 10, 1956, because of right-sided cardiac failure with marked dyspnea, cardiac enlargement, peripheral edema, abnormal electrocardiogram, and fluid at the lung bases. Figure 1 shows the chest film taken the same day. For the first time the azygos lobe was recognized, and the pear-shaped density in the right apex was noted and eventually identified as the arch of an abnormally situated azygos vein. Also seen clearly is the distended terminal portion of the vein. It is interesting to note the pleural fluid

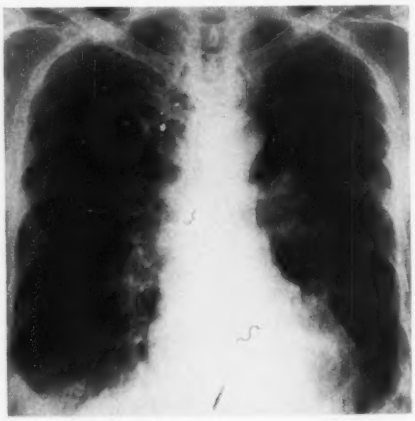

Fig. 1. January 27, 1956, 6-foot erect posteroanterior chest film. The distended azygos vein and the pear-shaped arch of the vein are seen in the first right anterior interspace; the curved hairline shadow in the right apex represents the fissure of the anomalous azygos vein. Pulmonary congestion, fluid at both bases, and enlargement of the heart suggest congestive failure.

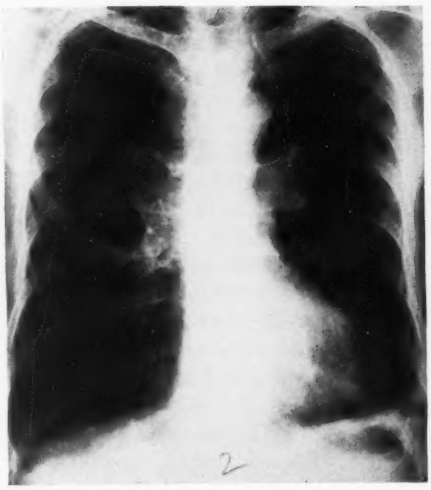

FIG. 2. February 6, 6-foot erect posteroanterior chest film. The distention of the azygos vein and its arch has disappeared; the heart is much smaller and the fluid at the bases is clearing. At this stage patient was practically free of congestive failure.

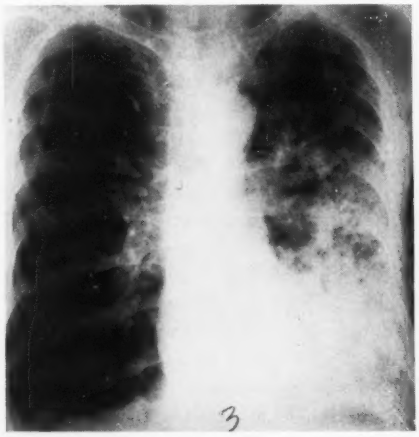

FIG. 3. March 7, 6-foot erect posteroanterior chest film. The slight increase in the size of the azygos vein and fluid in the right costophrenic angle suggest mild cardiac failure. A pneumonic process is noted at the left base.

long with the distention of the vein, since the arietal pleural veins drain into the azygos through e intercostal veins. By February 7, the patient as much better; he had lost 20 pounds of weight d was practically free of congestive failure. The enous pressure was 7 cm. of water and Decholin rculation time was 16 sec. The chest film at this me (fig. 2) is similar to the one of March 1954.

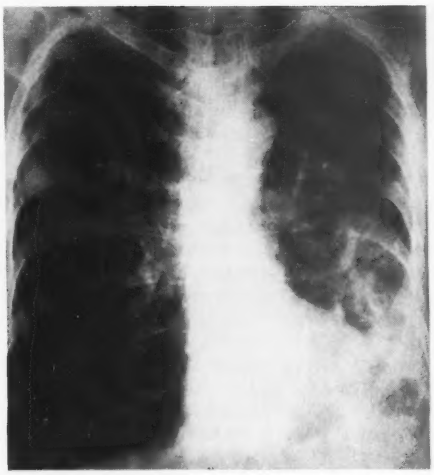

FIG. 4. March 15, erect posteroanterior 6-foot chest film in inspiration. The curved hairline shadow of the fissure of the azygos vein is in the first right anterior interspace with the small pear-shaped shadow of the arch of the vein at the lower end of the curved line. A pneumonic process is at the left base. The azygos vein is smaller and the fluid at the right base has disappeared, suggesting recovery from cardiac failure.

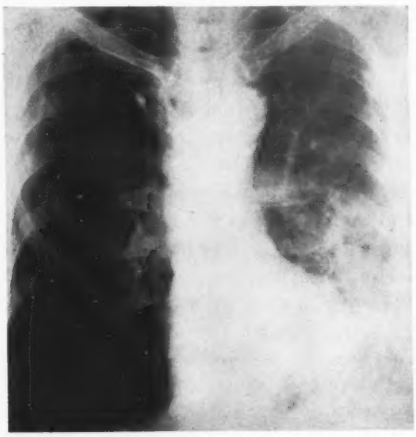

FIG. 5. March 15, 6-foot posteroanterior chest film with patient in 45-degree Trendelenburg position, in inspiration. In comparison with figure 4, this film shows significant distention of the arch of the azygos vein and the terminal portion of the vein leading from the arch to the superior vena cava.

Along with the disappearance of the distention of the azygos vein, the heart became normal in size, and the fluid at the bases practically disappeared.

The third admission was on March 7, 1956, for pneumonia. Physical examination showed signs of a

pneumonic process at the left base, but the evidence for congestive failure was not conclusive. X-ray films (fig. 3) showed that the azygos vein was slightly increased in size and that there was a reaccumulation of fluid at the right base, suggesting mild right-sided heart failure. There was also a pneumonic process at the left base. On March 15 the patient was improved, and roentgenograms were taken in erect, supine, and 45-degree Trendelenburg positions, both during expiration, inspiration, and Valsalva procedure. During inspiration in erect position (fig. 4) the azygos vein was thinner and the fluid at the right base had disappeared, suggesting the disappearance of congestive failure. In the 45-degree Trendelenburg position and full inspiration (fig. 5) the terminal part of the azygos vein and its arch were significantly distended, just as in figure 1 when the patient was in right-sided failure. This distention disappeared as soon as the patient assumed the erect position. Distention of the azygos vein and its arch was less in the horizontal prone position than in the Trendelenburg position. In the Trendelenburg position the Valsalva procedure and expiration did not materially change the size of the vein.

Discussion

Although described in the literature as visible in a large percentage of chest films,[3] in our experience the normally situated azygos vein is not easily recognized. Indeed, many current textbooks on cardiology and x-ray diagnosis do not refer to the normal azygos vein among the structures forming the right cardiac border. Even when this density is recognized as a vascular shadow, its differentiation from an enlarged lymph node is difficult. When distended in heart failure, it may even be more difficult to identify because of concomitant distention of the superior vena cava and pulmonary veins. On the other hand, the aberrant azygos vein is easily seen on posteroanterior chest films. The presence of the azygos lobe and the fissure of the vein make its recognition easier. The curved hairline shadow of the fissure of the vein is easily noted, as well as the comma or the pear-shaped density at its lower end. Both these structures are placed considerably lateral to the right border of the heart and the great vessels, and therefore are clearly visible. The shadow should not be confused with a lymph node or an infiltrative lesion of tuberculosis. It should be kept in mind that the azygos vein becomes distended in situations with an elevated systemic venous pressure such as right-sided heart failure, obstruction of the superior vena cava, or obstruction of the inferior vena cava, as well as in portal venous hypertension. The distention of the azygos vein in obstruction of the inferior vena cava or portal vein is due to the presence of venous anastomoses between the azygos vein and the collateral tributaries of the inferior vena cava and the portal vein. In the case reported in this paper, an abnormally situated azygos vein became distended during right-sided heart failure and disappeared after recovery. These changes parallel fluctuations of the venous pressure. Distention and its relief were also demonstrated in various positions, again paralleling fluctuations of venous pressure. Distention of an abnormally situated azygos vein, which is readily recognized radiologically, should be considered a sign of increased venous pressure in the superior and inferior venae cavae and the portal venous system.

Summary

The aberrant azygos vein is easily recognizable on posteroanterior chest films, while the normally situated vein is difficult to identify.

A case is reported in which distention of an aberrant azygos vein was demonstrated radiologically during periods of right-sided heart failure. The distention disappeared when the patient recovered from heart failure.

Distention of the vein was demonstrated radiologically in the supine and Trendelenburg positions when the patient was free of heart failure. Distention was more marked in the Trendelenburg position.

Early right-sided failure may be identified by the demonstration of distention of an aberrant azygos vein.

The aberrant azygos vein provides the clinician with an unusual sign that can focus attention upon increased venous pressure in the superior and inferior venae cavae and the portal vein.

Summario in Interlingua

Le aberrante vena azygos es facilemente recognoscibile in pelliculas thoracic posteroanterior. In su sito normal illo es difficile a identificar.

Es reportate un caso in que distension de un aberrante vena azygos esseva demonstrate radiologicamente durante periodos de disfallimento dextero-cardiac. Le distension dispareva quando le patiente se restabliva ab le disfallimento cardiac.

Le distension del vena esseva demonstrate radiologicamente in le position supin e in le position de Trendelenburg quando le patiente esseva libere de disfallimento cardiac. Le distension esseva plus marcate in le position de Trendelenburg.

Precoce disfallimento al latere dextere pote esser identificate per le demonstration de distension de un aberrante vena azygos.

Le aberrante vena azygos provide al clinico signos inusual que pote traher su attention al presentia de augmentate pressiones venose in le venas cave superior e inferior e in le vena portal.

REFERENCES

[1] Crane, A. W.: Inverted comma sign in pulmonary roentgenology. Am. J. Roentgenol. **5:** 124, 1918.

[2] Ottonello, P.: La rappresentazione radiografica dell'azygos in sede normale (aspeto a virgola rovesciata). Lotta contro tuberc. **2:** 1323, 1931.

[3] Stauffer, H. M., Labree, J., and Adams, F. H.: The normally situated arch of the azygos vein; its roentgenologic identification and catheterization. Am. J. Roentgenol. **66:** 353, 1951.

[4] Grant, J. C. B.: A Method of Anatomy, Ed. 4, Baltimore, The Williams & Wilkins Co., 1948, pp. 516, 526, 569.

[5] Twining, E. W., and Kerley, P.: The lobes and interlobar fissures of the lungs. *In* A Textbook of X-ray Diagnosis by British Authors. Edited by S. C. Shanks and P. Kerley. Ed. 2, vol. 2. Philadelphia and London, W. B. Saunders Co., 1951, p. 244.

[6] Joselevich, M., and Mactas, B. A.: La imagen radiologica del cayado de la vena acigos en las afecciones cardiovasculares. Rev. argent. cardiol. **2:** 96, 1944.

[7] Gemignani, V.: Il quadro radiologico stratigrafico dell'arco della vena grande azigos. Radiol. med. **32:** 381, 1946.

[8] Durieu, H., and Laguime, J.: Aspects radiologiques de la veine azygos au cours de l'insuffisance cardiaque. Arch. mal. coeur **31:** 609, 1938.

[9] Gray, H.: Anatomy of the Human Body. Ed. 25. Philadelphia, Lea and Febiger, 1950, pp. 676, 686.

[10] Anson, B. J.: An Atlas of Human Anatomy. Ed. 1. Philadelphia and London, W. B. Saunders Co., 1950, p. 202.

Dembowski, U., Hasse, H. M., and Köble, H.: Complications During Angiography. Ztschr. Kreislaufforsch. **44:** 959, 1955.

Complications appeared in 6 of 650 angiographies. In 1 case extensive cutaneous necroses appeared after injection of oxygen and dye, in 1 case transient paralytic ileus resulted from aortography, and in 2 cases thrombosis and embolism appeared. In 2 cases reversible cerebral damage was seen after aortography or angiography of the subclavian artery.

Lepeschkin

Widespread and Sudden Occlusion of the Small Arteries of the Hands and Feet

By R. P. JEPSON, F.R.C.S.

This paper analyzes the syndrome of symmetrical digital gangrene that results from various pathologic processes. If a group of such patients is closely studied, it is apparent that among those who have suffered a sudden and widespread occlusion of the small arteries of the hands and feet some may be grouped apart by reason of the single nature of the attack and the good prognosis. Eleven such examples seen by the author are described and their differential diagnosis, causation, and treatment discussed.

FOLLOWING Raynaud's[1] thesis in 1862 many case histories of minor and major limb gangrene have been selectively described as "symmetrical digital gangrene" because of the bilateral nature of the lesions. This term is not entirely satisfactory. It is apparent that the separation of "symmetrical digital gangrene" from other forms of limb gangrene is, in many ways, artificial and that it is a clinical presentation common to many different disease processes (table 1). In addition, in many cases, sudden occlusion of the small peripheral arteries may cause profound ischemia with cyanosis rather than tissue necrosis and the term "symmetrical digital gangrene" cannot be strictly applied to this less severe group. Among patients who have suffered a widespread and sudden occlusion of the small arteries of the hands and feet, with and without gangrene, some may be grouped apart by reason of the good prognosis that the disease carries and the absence of any etiologic factor. In this paper 11 such examples are described of digital gangrene or profound cyanosis of sudden onset occurring in 2 or more limbs; many of these have been reviewed for periods up to 15 years after the acute illness, and something of the natural history of the condition is described. Some of the more severely affected patients resemble those described by Raynaud[1] under the title of "symmetrical gangrene of benign form": Lewis and Pickering[2] added further case histories of "bilateral gangrene of digits in the young and with infection" and comprehensively reviewed the subject to that date.

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CLINICAL DATA

A history of normal health for years prior to the occlusive episodes was common to all the patients and more especially none had noticed "white fingers" or hemoglobinuria following exposure to cold. Physical examination failed to reveal any evidence of systemic disease although 4 of the patients had an associated pyrexia; Wassermann reactions and tests for autohemagglutination[3] were negative. The reactive hyperemia test[4, 5] and arteriography were used to define the pattern of occlusion in the hand and finger arteries.

Group A. Arterial Thromboses Associated with Pyrexial Illness (4 patients)

Case 1. Female, aged 2 years. This child had been admitted to the hospital 2 months prior to the vascular episode with a persistent pyrexia (100–101 F.) and raised erythrocyte sedimentation rate for which no reason could be found. The onset of the vascular lesions was heralded by bluish mottled patches over the outer side of the left foot. Within 24 hours both feet were cold, blue, and edematous and the ankle pulses were not palpable, although the popliteal pulses could be easily elicited. The right and, to a lesser degree, the left hand were similarly cold, cyanosed, and swollen. The right radial pulse could not be detected, although the brachial blood pressure in that arm was 120/70 mm. Hg. Within the next few days the fifth toe on the left foot became gangrenous and was finally amputated. A small necrotic area separated from the top of the right index finger. A tibial muscle biopsy was histologically normal, and arteriography failed to demonstrate any occlusion in the major vessels proximal to the ankles. Over the next few days all the major pulses returned to their normal volume and the limbs recovered normal warmth and color. When seen 5 years later the child was i

TABLE 1.—*Some of the Diseases That Have Been Described in Conjunction with Symmetrical Digital Gangrene*

Associated Disease:	
Arterial disease	Atherosclerosis,[7, 2] embolism, dissecting aneurysm, thromboangiitis obliterans, rheumatic arteritis.[8]
Infections	Pneumonia,[9] meningococcal meningitis,[10] cholera,[11] diphtheria,[6] tuberculosis,[12] syphilis,[6] fever of unknown origin.[2]
Thrombophlebitis	Idiopathic,[13] secondary to neoplasia.[14]
Cardiac lesions	Congestive heart failure,[10] mitral ball-valve thrombosis,[11] tight mitral stenosis,[11] myocardial infarction,[11] paroxysmal tachycardia,[11] endocarditis.[11]
Blood diseases	Cryoglobulinemia,[12] autohemagglutination,[15] hemoglobinuria.[2]
Physical causes	Frost-bite.
Miscellaneous	Ergot,[2] carbon monoxide poisoning,[11] cachexia.[1]

excellent health, energetic, and agile. A reactive hyperemia test still showed a delayed return of color to all the digits. She suffered from blue and cold hands in the winter.

Case 2. Female, aged 2 years. For 10 days prior to admission to the hospital the child was noted to be unwell and was thought by her parents to have a "cold." On the fifth day of this illness the feet had become cold, blue, and swollen, and blood-filled blisters had appeared over the dorsum of the distal part of the foot.

On admission to the hospital the child was found to be well nourished, pyrexial (101–102 F.), with feet and hands cold, blue, and edematous. Neither the radial nor ankle pulses were palpable, and oscillometer readings above the ankle were 0. The brachial blood pressure was 130/75 mm. Hg. Within 24 hours the radial pulses returned and during the following 3 days the feet showed signs of a reactive hyperemia, becoming pink and hot. A small area of skin became necrotic on the dorsum of the right foot. When seen 3 years later the ankle pulses had not returned, the child at that time being healthy and growing normally.

Case 3. Female, aged 54 years. This previously healthy housewife developed a mild "pyrexia" while

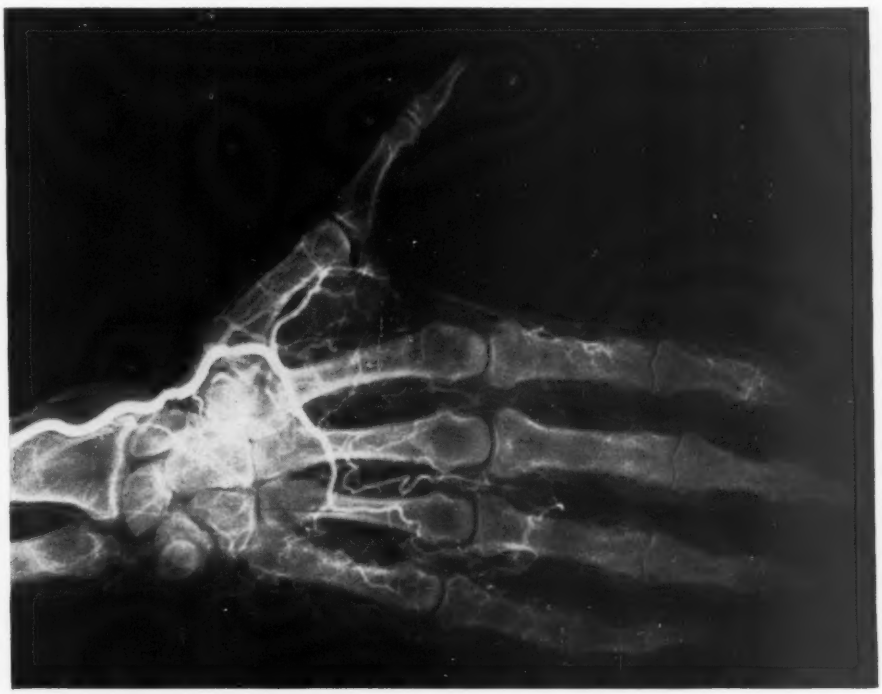

FIG. 1. Case 3. Arteriogram of left hand. Narrowing or occlusion of the digital arteries can be seen. The radial artery is slightly tortuous and it is probable that the ulnar artery is occluded.

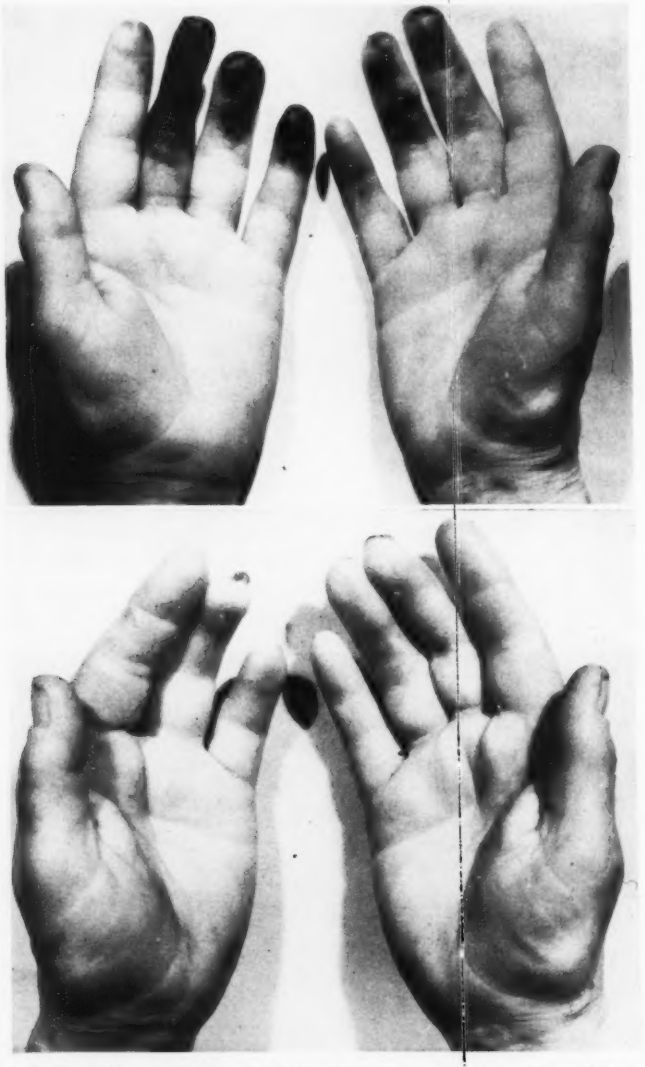

FIG. 2. Case 3. *Top*. The condition of the hands 7 days after the onset of illness. *Bottom*. The condition of the hands 2 months after the onset of illness.

on a holiday. On the third day of this illness all the fingers of the hands became cyanosed and painful within a matter of a few hours. When seen 48 hours later the fingers were blue and cold, and in the left little, middle, and index, and the right middle and ring fingers, the cyanosis spread proximally to the metacarpophalangeal joints. The reactive hyperemia test and arteriography demonstrated blocks in the arteries of all the digits together with normal patency of the slightly tortuous radial arteries. The left ulnar artery failed to fill and was probably occluded (fig. 1). Gangrene developed in the left middle finger, the distal part of which was amputated. Histology of the proximal digital vessels was described as showing a "bland" thrombosis with a slight degree of inflammatory reaction. A bilateral cervicothoracic ganglionectomy was performed, and the remaining fingers healed surprisingly well with only minimal skin loss over their pulps (fig. 2). At follow-up examination 7 years later the patient

complained of moderate cyanosis and occasional blanching of the fingers in cold weather but was otherwise well.

Case 4. Female, aged 67 years. This housewife developed cold blue hands and a pyrexia which lasted for a few days 6 months previous to examination. On examination, her fingers and thumbs were persistently cold and blue, the tip of the right middle finger being ulcerated. These were demonstrated by reactive hyperemia to be due to digital artery occlusion with a normal major circulation.

Group B. Acute Arterial Occlusions without Premonitory Symptoms (7 patients)

Case 5. Male, aged 23 years. This man had, up to his illness, worked as a farm laborer and as an Air Force private, occupations which had exposed his hands to all weathers without untoward effects. The illness developed 3 days previous to examination and, when first seen, both ears were blue and cold, the outer rims of each being black and gangrenous. These areas finally separated and the ears healed satisfactorily. In the hands all fingertips were dry, blackened, and anesthetic, with some patchy cyanosis proximally along the ulnar border of the arm and in the right thumb. All the toes on both feet showed gangrene at the tips and cyanosis. The peripheral major arteries in the 4 extremities were palpable and of normal volume.

A bilateral cervicothoracic and lumbar ganglionectomy were performed, following which the necrotic ends of the digits separated and healed within a few weeks. This patient returned to work as a farm laborer and has been seen at regular intervals for 10 years. During this period he has remained in perfect health except for gustatory sweating on the left side of the face and abnormal dryness of the hands, which may be attributed to the cervicothoracic ganglionectomy. He is free from Raynaud's phenomenon.

Case 6. Female, aged 54 years. This patient's history has unusual features in that premonitory episodes of localized gangrene preceded the bilateral attack (Lewis and Pickering[2]). In brief, the right forefoot became cyanosed in January, with loss by dry gangrene of the right little toe; in July of the same year the left big toe became cyanosed and gangrenous and was followed at intervals of a month by dry gangrene of the left second and third and the right fourth and fifth toes. In February of the following year all the digits of both hands became cyanosed and cold overnight; dry gangrene developed at the tip of all these, with separation and eventual healing. Bilateral cervicothoracic and lumbar ganglionectomies were performed. When reviewed 14 years later this patient (now aged 69) has remained perfectly well except that her hands are "cold" in the winter. Pulses remained normal at the wrist and ankle throughout.

Case 7. Female, aged 48 years. This housewife awakened one morning to find the little, ring, and middle fingers of both hands blue and painful; the index fingers were involved to a minimal degree but the thumbs were spared. Areas of patchy cyanosis up to several centimeters in diameter were apparent in both feet, particularly over the instep and toes. No other abnormal signs were detected, and all the major pulses were palpable. Following bilateral cervicothoracic ganglionectomy the fingers recovered their color and warmth, although a certain amount of subcutaneous wasting occurred in the pulps. After 5 years the patient remained well and free from further attacks.

Case 8. Female, aged 50 years. Her history is similar to case 7. All digits of 1 hand became cyanosed overnight, but recovered warmth and color on conservative therapy over the succeeding days with minimal ulceration of pulps. Her course was reviewed for 5 years, during which time she remained well.

Case 9. Female, aged 30 years. One week previous to examination the left index, middle, and little, and right middle, ring, and little fingers had become painful and cyanosed over their distal halves. She was otherwise free from any associated disease. The reactive hyperemia test demonstrated a gross delay (less than 20 sec.) in the time taken for the flush to reach the tips of all the digits. Over the next few weeks the fingers returned to a reasonable warmth and color without skin loss.

Case 10. Male, aged 7 years. In December this boy awakened one morning with all the fingers of both hands deeply cyanosed: to a lesser degree all his toes were likewise affected. There was no history of exposure to cold.

An arteriogram confirmed the abnormal reactive hyperemia test and demonstrated extensive thrombosis in the digital arteries, especially to the index fingers (fig. 3). The proximal arteries in the palm and arm were normal and patent. Following bilateral cervicothoracic ganglionectomy the fingers recovered their warmth and color. When reviewed 5 years later, the boy had grown and developed normally, and except for a moderate cyanosis of the fingers in very cold weather he experiences no disability.

Case 11. Female, aged 16 years. This girl developed a sudden and intense cyanosis and anesthesia of all the toes, which eventually resulted in the loss by dry gangrene of the lateral 3 digits in both feet. The hands were unaffected and both the posterior tibial and dorsalis pedis pulses were normal. Unfortunately, it has not been possible to follow the subsequent progress of this girl.

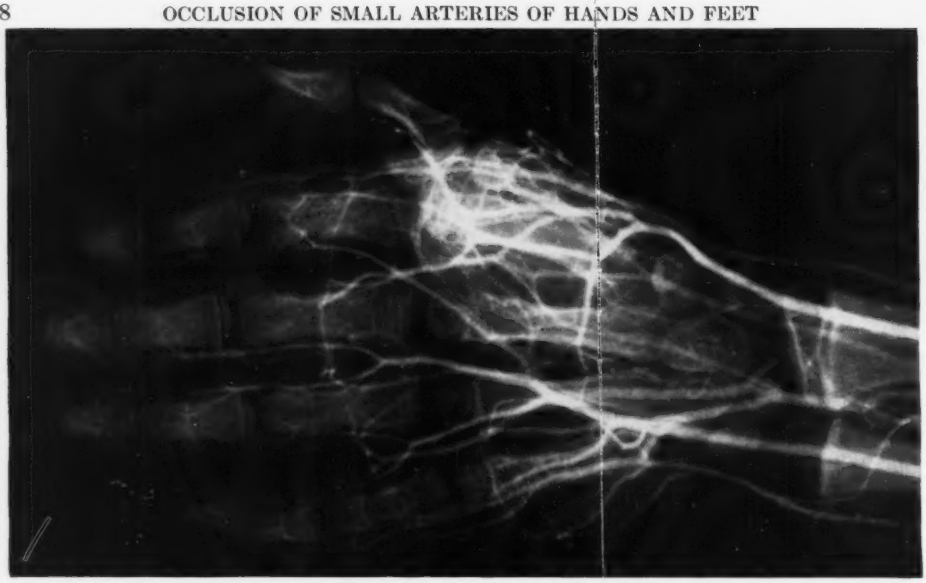

FIG. 3. Case 10. Arteriogram showing patency of radial and ulnar arteries but with multiple occlusions in the digital arteries.

DISCUSSION

Gangrene of the extremities that presents symmetrically is by no means uncommon; Morgan[6] collected 93 case reports from the literature and since that time many more have been added.[2] The majority of these have been clearly associated with some other disease processes (table 1), and can usually be excluded by clinical examination and by routine laboratory tests. When this is done, there remains a group of patients in whom an acute single illness is followed by a remarkable degree of recovery and it is suggested that, whereas the severe forms of this "benign" malady may reasonably be collected under the heading of "symmetrical digital gangrene," many, and possibly the majority, of the cases do not progress to gangrene. The diagnosis of digital artery occlusion as described in the present paper can only be irrevocably established on follow-up of the patients over a period of many years; it seems at present justifiable to group together such cases, whether they occur in infants or adults, with or without pyrexia, with gangrene or simply digital cyanosis.

All evidence from these patients points to the final lesion being a thrombotic occlusion of the digital or similar-sized arteries. The fingers clinically involved by cyanosis or gangrene consistently showed prolonged delay in the reactive hyperemia[5] and arteriography confirmed the presence of luminal occlusion. The arterial circulation as estimated by the blood pressure and palpable pulses at the wrist and ankle was adequate, with the exception of the 2 young girls (cases 1 and 2). In these the major pulses disappeared, later to return in 1 of them, suggesting that a prolonged arterial constriction was present early in the course of the disease. It is possible that the final occlusive lesions are secondary to a prolonged digital and more proximal arterial spasm, although there is no direct evidence to support this view. Histologic information is limited by reason of the minor forms of gangrene that were incurred; where it was obtained (case 3), the arterial wall showed only a mild inflammatory reaction to the luminal clot.

Whatever its etiology, the natural history of the disease was similar in all 11 patients. It presented as a single nonrecurrent episode (with the exception of case 6) that reached its maximum clinical severity early in its course.

The extremities at first sight appeared to be affected by such a profound ischemia that gangrene would certainly result. Experience proved otherwise; the collateral circulation, especially in the young, was rapidly established with recovery of deeply cyanosed and even anesthetic digital skin. Gangrene where it occurred was limited in extent and "dry."

In such cases where the digital lesions are not associated with any systemic disease, the patient may be assured that limb function will be little impaired and that the episode is unlikely to be repeated although Raynaud's phenomenon may appear in the involved fingers.

Summary

The case histories are presented of 11 patients in whom multiple arterial occlusions occurred, with or without an associated pyrexia, in the digits and ears. No evidence for an associated disease could be found in these patients. The organic occlusion of the digital arteries produced marked cyanosis of the digits, which in some instances proceeded to limited gangrene. It is suggested that similar cases of severer form have been previously described under the title of "symmetrical digital gangrene." The disease has not recurred in any of these patients who have remained well for periods up to 15 years.

Acknowledgment

My thanks are due to Professor A. M. Boyd, by whose courtesy many of these cases were seen.

Summario in Interlingua

Es presentate le historias de 11 patientes in qui occurreva multiple occlusiones arterial, sin o con associate pyrexia, in le digitos e in le aures. Nulle signo de morbo associate esseva detegibile in iste patientes. Le occlusion organic del arterias digital produceva marcate cyanosis del digitos, resultante, in certe casos, in gangrena limitate. Es postulate le possibilitate que simile casos de forma plus sever esseva previemente describite sub le termino de "symmetric gangrena digital." Le morbo non ha recurrite in le patientes del presente serie. Illes ha remanite libere de illo durante periodos de usque a 15 annos.

REFERENCES

1 Raynaud, M.: Selected Monographs: Trans. T. Barlow. The New Sydenham Society, London, 1938.

2 Lewis, T., and Pickering, G. W.: Observations upon maladies in which the blood supply to digits ceases intermittently or permanently, and upon bilateral gangrene of digits; observations relevant to so-called Raynaud's disease. Clin. Sc.: **1:** 327, 1933–4.

3 Forbes, G. B.: Autohaemagglutination and Raynaud's phenomenon. Brit. M. J. **1:** 598, 1947.

4 Pickering, G. W.: On the clinical recognition of structural disease of the periferal vessels. Brit. M. J. **2:** 1106, 1933.

5 Catchpole, B. N., Jepson, R. P., and Kellgren, J. H.: Peripheral vascular effect of cortisone in rheumatoid arthritis, scleroderma, and other related conditions. Ann. Rheumat. Dis. **13:** 302, 1954.

6 Morgan, J. E.: A case of Raynaud's symmetrical gangrene in a patient suffering from constitutional syphilis with some remarks on the history, nature and manifestation of the disease. Lancet **2:** 9, 64, 107, and 157, 1889.

7 Hutchinson, J.: Symmetrical acro-sphacelus without Raynaud's phenomena. Arch. Surg. **7:** 201, 1896.

8 Hunt, J. H.: The Raynaud phenomena: A critical review. Quart. J. Med. **5:** 399, 1936.

9 Storstein, O.: Incipient symmetrical peripheral gangrene complicating pneumonia. Brit. Heart J. **13:** 411, 1951.

10 Broders, A. C., Jr., and Snell, A. M.: Fulminating meningococcemia with gangrene. Am. J. Med. **3:** 657, 1947.

11 Cotton, R. T., and Bedford, D. R.: Symmetric peripheral gangrene complicating acute myocardial infarction. Am. J. Med. **20:** 301, 1956.

12 Wilensky, M. D., Fisher, M. M., Moldovan, A., and Gherardi, G. J.: Simultaneous quadrilateral gangrene. Arch. Surg. **67:** 557, 1953.

13 DeBakey, M., and Ochsner, A.: Phlegmasia cerulea dolens and gangrene associated with thrombophlebitis. Surgery **26:** 16, 1949.

14 Fisher, M. M., Hochberg, L. A., and Wilensky, N. D.: Recurrent thrombophlebitis in obscure malignant tumor of the lung. J.A.M.A. **147:** 1213, 1951.

15 Stats, D., and Bullowa, J. G. M.: Cold hemagglutination with symmetric gangrene of the tips of the extremities. Report of a case. Arch. Int. Med. **72:** 506, 1943.

Aorta-Pulmonary Artery Communication Through the Lungs

Report of a Case

By T. Sterling Claiborne, M.D., and William A. Hopkins, M.D.

A case is reported of anomalous communication between the aorta and pulmonary artery by way of a pulmonary vascular mass. The left-to-right shunt was sufficient to cause typical circulatory dynamics and was demonstrated by cardiac catheterization and angiography. Complete cure was obtained by lobectomy.

THIS paper presents a case of aortic pulmonary artery communication in the right lung, demonstrated by cardiac catheterization and angiocardiogram. Several types of blood vessel communications in the lungs are reported under various terms: pulmonary arteriovenous fistula, cystic disease of the lungs, anomalous pulmonary arteries, and sequestration of the lung.[1-7] While some of these are obviously different disorders, others are closely related to each other. The direction and amount of blood flow in such communications are the most important features from the cardiovascular standpoint. When the flow of blood is from the pulmonary artery to pulmonary vein, cyanosis occurs and bleeding from the bronchial tree is frequent. Cough may be experienced but the condition is often asymptomatic and first diagnosed by x-ray. X-ray films may reveal a characteristic rounded area of communication between the enlarged afferent and efferent vessels. A murmur may be heard over the lesion. The heart is usually unaffected. The blood pressure is normal and there is usually no flow from the aorta into the communicating vessels.

When a vessel arising from the aorta becomes a part of the pulmonary arteriovenous fistula, the hemodynamics may be greatly altered. The high systemic pressure blocks the flow of unsaturated pulmonary artery blood and cyanosis may be absent. Such a case was reported by Lawrence and Rumel in 1950.[5] Their patient had cardiac failure. The blood pressure was 140/70. At operation, in addition to a large 3 cm. pulmonary artery branch and 3 cm. pulmonary vein branch, a 0.75 cm. bronchial artery also entered the mass. The authors surmised that the supply of arterial blood directly from the aorta might have blocked cyanosis and questioned the role of this fistula in producing failure. Other cases have been reported of a branch entering from the aorta, but we have found no case with clinical studies and cardiac catheterization showing a free communication from the aorta to the pulmonary artery. Such a free communication would be expected to produce hemodynamic changes similar to patent ductus arteriosus or any peripheral high-pressure low-pressure fistula. In the case reported below the aorta communicated with the pulmonary artery through a pulmonary vascular mass. The clinical and laboratory evidence of increased load on the left ventricle was imposing and cure was accomplished by lobectomy.

From the Giddings Memorial Heart Clinic, St. Joseph's Infirmary, Atlanta, Ga.

Case Report

J. W. was a 14-year-old female student apparently in good health. There was a history of normal delivery without cyanosis and of normal activity without symptoms. She was last examined at age 9 by her pediatrician, who found no abnormalities.

In a routine school examination in September 1955 by Dr. Dewey Nabors a murmur was noted and further study was advised.

On October 4, 1955, she appeared healthy, normally developed, and without cyanosis. The lungs were normal on physical examination but a continuous machinery-like murmur was heard all over the chest, loudest to the right posteriorly. Anteriorly, the murmur was louder to the right than to the left of sternum. The blood pressure was 130/4[illegible] in both arms. The pulses in the femoral and dorsalis pedis arteries were forceful and bounding. Fluor-

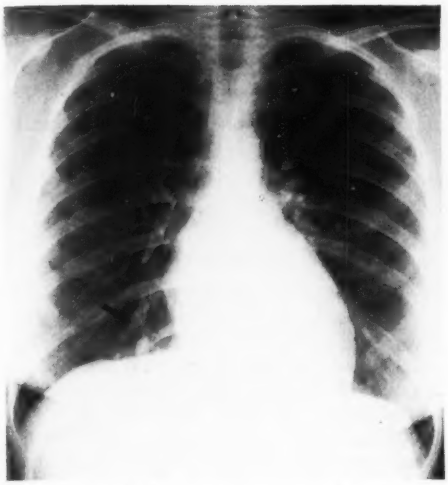

FIG. 1. X-ray showing prominent vessel at right base

scopic examination of the chest showed slight left ventricular enlargement. The markings at the right base were somewhat increased, but no pulsation could be seen. Roentgenogram showed slight enlargement of the right lower pulmonary artery (fig. 1).

On November 10, 1955, cardiac catheterization was done (table 1); a marked increase in the oxygen content in the right pulmonary artery established a communication between the aorta and pulmonary artery. We thought this was not a patent ductus because of the location of the murmur and the suspicious lesion on x-ray examination.

TABLE 1.—*Cardiac Catheterization Data November 10, 1955*

	Pressure	O_2 content vol. %
Superior vena cava		13.30
Right mid atrium	3 mm. Hg	13.38
Right atrium, high		13.26
Right ventricle	23/5 mm. Hg	13.00
Right ventricle		13.16
Right pulmonary artery	8/0 mm. Hg	16.56
Left pulmonary artery		14.15

Note the increased oxygen content in the pulmonary arteries, the right being higher than the left.

On December 3, 1955, angiography (fig. 2) demonstrated a large pool of dye in the right lower lung, which seemed to fill from the aorta and flow into the pulmonary artery.

On December 19, 1955, operation performed by Dr. William Hopkins disclosed an artery 1 cm. in diameter arising from the aorta and coursing through the pulmonary ligament into the right lower lobe. A strong thrill suggested a considerable blood flow. The entire surface of the right lower lobe was covered by small but injected blood vessels. The entire lower lobe was removed because it was thought that all the vessels communicated.

Injection of the specimen with contrast medium through the abnormal vessel demonstrated a communication with the pulmonary artery through the lower lobe. This represents an abnormal and unusual aorta-pulmonary artery communication. No evidence of sequestrated lung was present.

The patient recovered promptly without com-

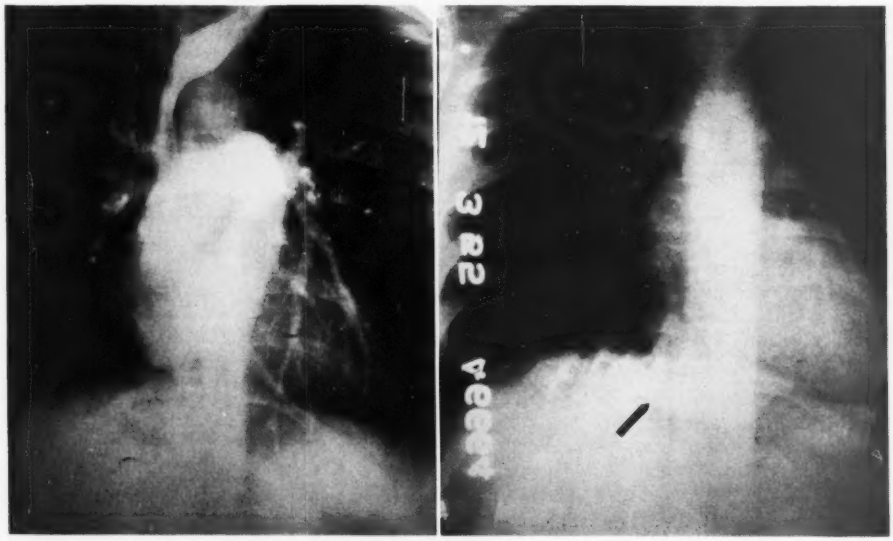

FIG. 2. Angiogram. Note the lack of opacification of lower part of right pulmonary artery at 5 sec. (left) and, at 15 sec. (right), the pooling of dye from aorta into base of right lung.

plications; no murmur or thrill was present after the operation. She is in school and active without symptoms. On recent fluoroscopic examination there was no heart enlargement. The blood pressure was 105/70 in February 1956, and 125/80 in May 1956.

Summary

Several cases of pulmonary arteriovenous communications have been reported in recent years with the blood flow from pulmonary artery to pulmonary veins. Such blood vessel masses may contain other vessels arising from the aorta with the hemodynamics of a high-pressure low-pressure shunt. A patient is reported with an aorta-pulmonary artery communication causing wide peripheral pulse pressure and increased load on the left heart. Catheterization and angiocardiographic studies demonstrated the shunt. Surgical cure was obtained by right lower lobectomy.

Summario in Interlingua

In recente annos, plure casos de communicationes arterio-venose pulmonar esseva reportate, con le fluxo sanguinee ab le arteria pulmonar verso le venas pulmonar. Tal massas de vasos sanguinee pote continer altere vasos, originari ab le aorta, con le hemodynamica de un shunt ab alte pression a basse pression.

Es reportate le caso de un patiente con u communication inter aorta e arteria pulmona , resultante in un large pression de pulso p ripheric e un augmento del carga del corc e sinistre. Catheterisation e studios angiocard - ographic demonstrava le shunt. Restitutic chirurgic esseva effectuate per medio de l - bectomia dextero-inferior.

REFERENCES

1. Smith, H. L., and Horton, B. T.: Arteriovenous fistula of lung associated with polycythemia vera: Report of a case in which diagnosis was made clinically. Am. Heart J. **18:** 589, 1939.
2. Watson, W. L.: Pulmonary arteriovenous aneurysm. Surgery **22:** 919, 1947.
3. Burchell, H. B., and Clagett, O. T.: The clinical syndrome associated with pulmonary arteriovenous fistulas. Am. Heart J. **34:** 151, 1947.
4. Maier, H. C., Himmelstein, A., Riley, R. L., and Bunim, J. J.: Arteriovenous fistula of the lung. J. Thoracic Surg. **17:** 13, 1948.
5. Lawrence, E. A., and Rumel, W. R.: Arteriovenous fistula of the lung. J. Thoracic Surg. **20:** 142, 1950.
6. Findley, C. W., Jr., and Maier, H. C.: Anomalies of the pulmonary vessels and their surgical significance. Surgery **29:** 604, 1951.
7. Mannix, E. P., and Haight, C.: Anomalous pulmonary arteries and cystic disease of the lung. Medicine **34:** 193, 1955.

Pure rationalism, complete immunity from prejudice, consists in refusing to see that the case before one is absolutely unique. It is always possible to treat the country of one's nativity, the house of one's fathers, the bed in which one's mother died, nay, the mother herself if need be, on a naked equality with all other specimens of so many respective genera.—William James, *Principles of Psychology*, 1842–1910.

Exchangeable Potassium Content of the Body in Congestive Failure

Changes During Treatment

By JERRY K. AIKAWA, M.D., AND REGINALD H. FITZ, M.D.

With the technical assistance of Aaron J. Blumberg

The increase in body weight in congestive heart failure is generally attributed to the retention of sodium and water in the extracellular compartment. Important changes also occur in the intracellular space, particularly in the metabolism of potassium. The isotope-dilution technic permits more precise determination of the exchangeable potassium content of the body in congestive failure before and during diuresis. The results of 27 such determinations in 11 patients with congestive heart failure are correlated with the clinical status of the patient and the serum concentration.

IT HAS generally been assumed that an increase in body weight that occurs during congestive heart failure is due to retention of sodium and water in the extracellular compartment. Recent studies, however, have suggested that changes also occur in the intracellular phase, and in the metabolism of potassium as well as sodium.[1-3] The external balance method, which has been used in most previous studies of this problem, does not permit the direct measurement in vivo of the body's potassium content. This difficulty can be overcome by the use of the isotope-dilution technic —a technic that has previously been applied to studies on the pathophysiology of other disease states.[4]

The purpose of the present study was to determine, by use of the in vivo isotope-dilution technic, changes in the exchangeable potassium content of the body during the therapy of congestive failure. Serial determinations of the exchangeable potassium content were made in hospitalized patients, and the changes in this value were correlated with the alterations in serum electrolytes, body weight, and the clinical response.

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This work was supported in part by grants-in-aid from the American Heart Association and Wyeth Laboratories, and in part under a contract with the U. S. Atomic Energy Commission.

Dr. Aikawa is an Established Investigator of the American Heart Association.

MATERIAL AND METHODS

Subjects. Eleven patients with advanced congestive failure, 8 men and 3 women, were studied. Their ages ranged from 48 to 83 years. In 4 subjects, the cause of the congestion was rheumatic heart disease; in 4 subjects, arteriosclerotic heart disease; in 2 subjects, pulmonary fibrosis and emphysema with cor pulmonale; and in 1 subject, syphilitic heart disease. Most of these individuals had previously been followed in the Outpatient Clinic and had received maintenance doses of digitalis, ammonium chloride, and aminophylline, and periodic injections of a mercurial diuretic. Only 1 patient (case 5) had not previously been treated with digitalis. When admitted to the hospital, all had gross edema.

The general plan was to make at least 2 determinations of the exchangeable potassium content, the serum concentrations of sodium and potassium, and the body weight during hospitalization. In some instances, 3 or more observations were made.

All patients received a diet containing not more than 400 mg. of sodium; water was given without restriction. A summary of the clinical data and the type of therapy employed is given in table 1.

Isotopes. Isotopic potassium (K^{42})* was prepared for injection in the manner previously described.[4]

Measurement of Radioactivity. The activity of the urine specimens was determined with a well-type scintillation counter and a scaling circuit. A total of 10,000 counts was made on each sample. All determinations were corrected for decay.

Determinations of Serum Sodium and Potassium. The sodium and potassium concentrations in the serum were determined with a Baird flame photometer, using the lithium internal standard method.

* K^{42} was supplied by the National Laboratory, Oak Ridge, Tennessee, on allocation from the U.S. Atomic Energy Commission.

TABLE 1.—*Body Weight, Exchangeable Potassium Content, and Serum Electrolytes During the Therapy of Congestive Failure*

Case	Age (Yrs.) Sex	Cause of congestion	Pertinent clinical data	Therapy between successive determinations of K_e	Days of hospitalization	Weight (Kg.)	Exchangeable potassium content		Serum concentration	
							Total (mEq.)	K_e/Wt. (mEq./Kg.)	Sodium (mEq./L.)	Potassium (mEq./L.)
1	82 M	ASHD	Increase of 13 Kg. in 1 month. 82.3 Kg. on admission	Digoxin; mercurial, 2 ml. × 1; KCl, 3 Gm. × 1	6	77.3	1878	25.3	152.1	4.1
					13	74.3	2757	37.1	149.1	3.9
					20	69.5	2058	29.6	138.6	4.5
2	67 F	RHD	85.5 Kg. on admission	Digitoxin; KCl, 3 Gm. daily × 6	8	69.5	1635	23.5	139.8	4.3
					15	65.5	1742	26.6	140.6	5.1
3	57 M	Cor. P.	NPN of 158 mg.% on admission; decrease to 74 mg.% with K_{e_2}	Digitoxin; mercurial, 1 ml. × 1	1	72.3	2655	36.7	135.5	4.9
					8	70.9	3341	47.1	138.7	4.7
4	55 M	ASHD	Progressive dyspnea, orthopnea, and edema for 2 mos. 86.4 Kg. on admission	Digitoxin; mercurial, 2 ml. × 6, 1 ml. × 3; NH_4Cl, 6 Gm. daily × 5	5	76.3	2018	26.4	146.5	5.7
					19	67.5	2505	37.1	149.1	4.9
5	50 M	Cor. P.	Progressive dyspnea, orthopnea, and edema for 4 mos. 77.3 Kg. on admission	Digitoxin; aminophylline; mercurial, 2 ml. × 1; KCl, 6 Gm. daily × 8	6	63.6	2193	34.5	—	4.6
					13	60.5	2349	38.8	135.1	5.7
6	76 M	Syph. H. D.	Progressive dyspnea and edema for 2 mos. 55.5 Kg. on admission	Digitalis	6	51.0	1816	35.6	138.8	5.0
					13	48.6	2105	43.3	141.6	5.5
7	83 M	ASHD	Chronic congestion for 1 yr.; progressive edema for 1 mo. 63.2 Kg. on admission	Digitalis; mercurial, 2 ml. × 3, 1 ml. × 1; NH_4Cl, 6 Gm. × 1	6	62.3	1710	27.5	150.2	5.7
					20	56.8	1255	22.1	135.5	5.3
8	65 M	RHD	Chronic with intermittent acute congestive failure; atrial flutter	Gitalin; mercurial, 2 ml. × 2	2	66.4	2235	33.7	136.8	4.8
					9	64.0	1926	30.1	133.7	5.1
9	66 M	ASHD	Progressive failure for 3 mos.; pulmonary infarct on 11th hospital day. 90.0 Kg. on admission		5	82.1	2626	32.0	143.3	4.9
				Digitalis; mercurial, 2 ml. × 1	12	76.9	2071	26.9	129.7	5.0
				Digitalis, NH_4Cl, 8 Gm. × 3	26	72.3	2441	33.7	137.0	5.7
				Digitalis	33	73.9	2526	34.2	145.2	4.8
				Digitalis	54	76.4	2587	33.9	134.8	5.9
10	59 F	RHD	Dyspnea and edema, 4 mos.; worse with chest pain for 1 wk.; old and recent pulmonary infarctions; died on 28th day	Digoxin	3	112.9	2415	21.4	137.2	4.9
				Digoxin, Diamox	10	109.3	2307	21.1	140.6	4.8
				Digoxin, NH_4Cl; KCl	24	—	2171	—	131.4	5.5
11	48 F	RHD	Progressive decompensation for 15 yrs.; recent weight gain and resistant failure. 47.7 Kg. on admission	Digitalis	16	51.4	1106	21.5	135.9	4.7
				Digitalis	23	53.2	1383	26.0	141.8	4.4

ASHD = arteriosclerotic heart disease; RHD = rheumatic heart disease; Cor. P. = cor pulmonale; Syph. H. D. = syphilitic heart disease.

Determination of Exchangeable Potassium Content (K_e). Each subject received from a calibrated syringe an intravenous injection of 1.5 μc. of K^{42}/Kg. of body weight. All urine voided thereafter until 6 a.m. the following day was collected, and the K^{42} content of the pooled specimen was determined. Determinations of the specific activity were made on 3 spot samples of urine obtained at 8, 9, and 10 a.m. the day after injection.

The mathematical calculation of the value for the exchangeable potassium content of the body has been described in detail previously.[4, 5]

Preliminary studies in this laboratory confirmed the observations of Corsa and his associates[5] that the specific activity of K^{42} in the urine reaches an equilibrium in both diseased and normal subjects within 18 hours. The mean difference in specific activity among the 3 spot specimens, when expressed as percentage of the mean K_e, was 4.57 ± 2.76 per cent. In another group of 11 hospitalized subjects who were in a steady state, 2 K_e determinations made in this laboratory within a period of 2 weeks agreed within a mean of 2.12 ± 1.10 per cent.

Results

A total of 27 K_e determinations was made—2 determinations on each of 8 individuals, and more than 2 in the remaining 3 patients. The determinations were made at the intervals specified in table 1.

Table 2.—*Changes in Exchangeable Potassium Content, Serum Electrolytes, and Body Weight During the Therapy of Congestive Failure*

Case	Day of hospitalization	Change in weight*		Change in exchangeable potassium*		Change in serum sodium* (mEq./L.)	Change in serum potassium* (mEq./L.)
		(%)	(Kg.)	(%)	(mEq.)		
1	13	−3.9	−3.0	+46.8	+879	−3.0	−0.2
	20	−10.1	−7.8	+9.6	+180	−13.5	+0.4
2	15	−5.8	−4.0	+6.5	+107	+0.8	+0.8
3	8	−1.9	−1.4	+25.8	+686	+3.2	−0.2
4	19	−11.5	−8.8	+24.1	+487	+2.6	−0.8
5	13	−4.9	−3.1	+7.1	+156	—	+1.1
6	13	−4.7	−2.4	+15.9	+289	+2.8	+0.5
7	20	−8.8	−5.5	−26.6	−455	−14.7	−0.4
8	9	−3.6	−2.4	−13.8	−309	−3.1	+0.3
9	12	−6.3	−5.2	−21.1	−555	−13.6	+0.1
	26	−11.9	−9.8	−7.0	−185	−6.3	+0.8
	33	−10.0	−8.2	−3.8	−100	+1.9	−0.1
	54	−6.9	−5.7	−1.5	−39	−8.5	+0.1
10	10	−3.2	−3.6	−4.5	−108	+3.4	−0.1
	24		—	−10.1	−244	−5.8	+0.6
11	23	+3.5	+1.8	+25.0	+277	+5.9	−0.1

* Compared with value obtained at time of first exchangeable potassium determination.

Table 3.—*Summary of the Direction of Changes in Weight, Exchangeable Potassium Content, and Serum Electrolytes During the Therapy of Congestive Failure*

Case	Weight	Exchangeable Potassium	Serum Sodium	Serum Potassium	Clinical Response
1–6	↓	↑	↑*	—	Satisfactory
7	↓	↓	↓	—	Satisfactory
8	↓	↓	↓	—	Protracted convalescence
9	↓	↓	↓	—	Protracted convalescence, pulmonary infarction
10	↓	↓	↓	—	Pulmonary infarction, died
11	↑	↑	↑	—	Protracted convalescence

↑ = increase, ↓ = decrease, — = no significant change.

* Case 1 showed a decrease in serum sodium concentration.

The reported range for K_e in normal men is 2770–4470 mEq. with a mean of 3402 mEq., or 35.6–55.6 mEq./Kg. with a mean of 46.3 mEq./Kg.[5] For normal women the range in 1 series[6] was 1374–2164 mEq. with a mean of 1776 mEq., or 25.1–35.9 mEq./Kg. with a mean of 31.5 mEq./Kg.; in another series[7] it was 28.6–47.2 mEq./Kg. with a mean of 40.7 mEq./Kg.

In the present study, all initial values for K_e in the men was below the normal range, although only 1 of the 3 women showed a subnormal value. The initial ratio of exchangeable potassium content to weight (K_e/wt.) was below the normal range in all cases except 2 (cases 3 and 6). The lowest initial value for K_e/wt. (21.4 mEq./Kg.) was found in a woman who subsequently died in congestive failure, with complicating old and new pulmonary infarctions (case 10).

All subjects except 1 (case 11) lost weight in the period between the first and second K_e determinations. The mean loss was 4.5 Kg., the range 1.4–8.8 Kg. One subject (case 11) gained 3.7 Kg. in weight during the first 16 days of hospitalization, before the first K_e determination was made, and gained an additional 1.8 Kg. during the 7-day interval between the 2 determinations of K_e.

The patients may be rather arbitrarily divided into 2 groups on the basis of the clinical course.

Group 1. Seven patients showed a satisfactory clinical course with diuresis, weight loss, and amelioration of symptoms and signs. In 6 of these subjects (cases 1–6) the average increase in K_e was 318 mEq. (range, 107–686 mEq.), while the average decrease in body weight was 4.6 Kg. (range, 1.4–8.8 Kg.). This mean increase in K_e amounted to 15.6 per cent of the initial value, whereas the mean decrease in body weight was 6.7 per cent of the mean initial value.

None of these subjects showed a marked change in the concentration of serum sodium or potassium between the first 2 determinations of K_e, although the serum sodium concentration tended to rise slightly as the K_e increased. In 1 subject, (case 1) a third determination of K_e was made 1 week after the second. At this time the body weight had decreased an additional 4.8 Kg., but the K_e value, while still higher than the initial determination, was 699 mEq. lower than the second observation. The serum sodium concentration had decreased from 149 to 139 mEq./L., although the serum potassium concentration remained within the normal range.

The seventh patient (case 7) responded satisfactorily to treatment, but the K_e decreased by 455 mEq. and the weight by 5.5 Kg.; the serum sodium decreased 15 mEq./L., from 151 to 136 mEq./L.

Group 2. Four patients did not show a satisfactory clinical course. One patient (case 8) had a limited diuresis during the period of study, but did not respond satisfactorily until an atrial flutter was subsequently converted to normal sinus rhythm. The course of 1 patient (case 9) was complicated by repeated pulmonary infarctions. The third patient (case 10) died with old and new pulmonary infarctions. All 3 of these patients lost weight and showed a decrease in the K_e and in the serum sodium concentration; the serum potassium concentration did not change.

In only 1 instance (case 11) did both the body weight and the K_e increase during the period of observation. In this patient the initial value for serum sodium was low, and it increased between the 2 K_e determinations; the serum potassium concentration remained unchanged.

Discussion

Previous studies on the pathophysiology o electrolyte and water metabolism in congestiv failure have been hampered by the lack of suitable method for measuring changes in th intracellular compartment. The isotopic dilu tion technic makes it possible to measure, d rectly in the living subject, changes in the ex changeable body content of potassium ion which is located predominantly within th cells. The technic is relatively simple and con venient; the measurements are reproducible t a striking degree, and rather small changes i the body content of potassium (of the order o 100 mEq.) can be detected.

Changes in Exchangeable Potassium (K_e). A low value for K_e/wt. may be expected whenever there is an increase in the relative fat content or in the extracellular fluid and electrolytes (that is, a relative decrease in cell mass). A low *absolute* value for K_e will occur when muscle mass is decreased, or when there is a depletion of intracellular potassium in the presence of a relatively normal or low cell mass. In an edematous subject, a low value for K_e/wt. and a concomitant low absolute value for K_e suggest a depletion of intracellular potassium, a decrease in lean muscle mass, or both, in association with a relative increase in the volume of extracellular fluid.

The value for exchangeable potassium per kilogram may rise simply with a loss of body water, but the changes observed in this moiety were considerably greater than could be accounted for by water loss alone. Six of the 7 patients who improved clinically during the present study showed an increase in the *absolute* value for exchangeable potassium content at a time when the body weight decreased and diuresis occurred. This sequence suggests either that lean tissue mass actually increased as the patients improved, or that a depletion of intracellular potassium had occurred as congestive failure developed. Squires, Crosley, and Elkinton,[1] in their study of the same problem by the external metabolic balance method, have shown that the positive potassium balance that de

velops during therapy of congestive failure is out of proportion to the increase in nitrogen balance—a finding that suggests a prior depletion of potassium. The relative magnitude of positive potassium balance observed in their study was comparable to the increase in exchangeable potassium content found in the present study. Similar results have also been obtained by other investigators using the external balance method.[2, 3, 8, 9]

It has been previously reported that the failing heart is depleted of potassium to an extent that is dependent upon the degree of myocardial insufficiency,[10, 11] and that this depletion of potassium is shared by other body tissues such as skeletal muscle.[12] The results of the present study give quantitative expression to this impression. This intracellular depletion of potassium, amounting to a maximum of 32 per cent of the estimated normal exchangeable body content (case 1) was not accompanied by a decrease in the serum potassium concentration. Previous studies in other disease states, however, have suggested than an *acute* depletion of exchangeable potassium in excess of 25 per cent of the total body content is necessary before clinical symptoms and signs of hypokalemia appear.[13] In a disease that develops as gradually as does congestive failure, it is probable that a considerably greater depletion can be tolerated before clinical manifestations of deficiency occur.

In 1 of the 7 subjects who showed a satisfactory response to therapy (case 7), the K_e decreased by 455 mEq. as the body weight decreased by 5.5 Kg. This patient received a total of 280 mg. of mercury between the 2 determinations, and the potassium depletion was probably caused by the renal effect of this amount of organic mercurial.[9, 14] It should be noted, however, that another patient in this series (case 4) had received considerably more mercury (600 mg.); yet his K_e increased by 487 mEq. as his body weight decreased by 8.8 Kg. Thus the administration of mercurial per se may not necessarily lead to potassium depletion.

The results of the K_e studies in 3 of the 4 subjects who responded poorly to treatment (cases 8–10) are compatible with the interpretation that a complication such as pulmonary infarction produces a further decrease in K_e (because of death of tissue), and an increase in intracellular potassium deficiency as congestive failure is secondarily aggravated. In the fourth subject (case 11) the simultaneous increase in K_e, body weight, and serum sodium concentration has been interpreted as the resultant of increase in lean tissue mass and correction of a prior intracellular depletion of potassium. This patient was markedly undernourished on admission, and her appetite improved while she was hospitalized.

The results of the present study suggest that patients with congestive failure that advances in spite of treatment have an absolute deficit in intracellular potassium content; that this deficit may not necessarily be reflected by a concomitant decrease in extracellular potassium concentration; and that the intracellular potassium content usually returns toward normal as clinical improvement occurs. Previous observations[15] have shown that the decrease in body weight during therapy of congestive failure usually exceeds the relative decrease in exchangeable sodium content. These data are compatible with the hypothesis that congestive failure is characterized by intracellular potassium deficiency and by intracellular as well as extracellular overhydration. Further studies are indicated in order to determine more specifically the nature of the fluid and electrolyte disturbances in congestive failure.

Summary

The in vivo radioisotopic dilution technic was used to follow the changes in the exchangeable potassium content (K_e) of 11 hospitalized patients with congestive failure.

Nine of 11 initial values for K_e and K_e/wt. were below the normal range. In 6 of 7 patients who responded satisfactorily to therapy, K_e increased by a mean of 318 mEq. at a time when weight decreased by a mean of 4.6 Kg. Serum electrolyte concentrations showed no striking changes in these patients. The seventh patient showed a decrease of 455 mEq. in K_e and 5.5 Kg. in weight; serum sodium decreased by 15 mEq./L.

In the 4 patients whose clinical response was

unsatisfactory, the changes in K_e were thought to be the result of complications.

It is concluded that the body store of potassium that can exchange with K^{42} is depleted during congestive failure and replenished when response to treatment is satisfactory. A complication or an increase in the severity of failure is accompanied by a further decrease in exchangeable potassium.

Summario in Interlingua

Le technica de dilution radioisotopic in vivo esseva usate pro traciar le alterationes del contento de kalium excambiabile (K_e) in 11 patientes hospitalisate con disfallimento congestive.

Nove del 11 valores initial pro K_e e pro K_e/peso esseva infra le nivellos normal. In 6 inter 7 patientes con satisfacente responsas al therapia, K_e se augmentava per un valor medie de 318 mEq a un tempore quando le peso se diminueva per un valor medie de 4,6 kg. Le concentrationes del electrolytos seral monstrava nulle frappante alterationes in iste patientes. Le septime patiente monstrava un reduction de 455 mEq in K_e and de 5,5 kg in peso. Le natrium seral decresceva per 15 mEq/l.

In le 4 patientes in qui le responsa clinic non esseva satisfactori, le alterationes in K_e esseva considerate como resultato de complicationes.

Nos conclude que le stock corporee de kalium excambiabile con K^{42} es reducite in disfallimento congestive e replenate quando le responsa al therapia es satisfacente. Un complication o un augmento del grado de severitate del disfallimento es accompaniate per un reduction additional del kalium excambiabile.

REFERENCES

[1] Squires, R. D., Crosley, A. P., and Elkinton, J. R.: The distribution of body fluids in congestive heart failure. III. Exchanges in patients during diuresis. Circulation **4:** 868, 1951.

[2] Iseri, L. T., Boyle, A. J., and Myers, G. B.: Water and electrolyte balance during recovery from severe congestive failure on a 50 milligram sodium diet. Am. Heart J. **40:** 706, 1950.

[3] Sinclair-Smith, B., Kattus, A. A., Genest, J. and Newman, E. V.: The renal mechanism o electrolyte excretion and the metabolic balance of electrolytes and nitrogen in congestive cardia failure; the effects of exercise, rest and amino phyllin. Bull. Johns Hopkins Hosp. **84:** 369 1949.

[4] Aikawa, J. K., Felts, J. H., Jr., Tyor, M. P., an Harrell, G. T.: The exchangeable potassiu content in disease states. J. Clin. Invest. **31** 743, 1952.

[5] Corsa, L., Olney, J. M., Steenburg, R. W Ball, M. R., and Moore, F. D.: The measure ment of exchangeable potassium in man by iso tope dilution. J. Clin. Invest. **29:** 1280, 1950.

[6] Aikawa, J. K., Harrell, G. T., and Eisenberg B.: The exchangeable potassium content of nor mal women. J. Clin. Invest. **31:** 367, 1952.

[7] Edelman, I. S., Olney, J. M., James, A. H., Brooks, L., and Moore, F. D.: Body composition: Studies in the human being by the dilution principle. Science **115:** 447, 1952.

[8] Miller, G. E.: Water and electrolyte metabolism in congestive heart failure. Circulation **4:** 270, 1951.

[9] Schwartz, W. B. and Wallace, W. M.: Observations on electrolyte balance during mercurial diuresis in congestive heart failure. J. Clin. Invest. **29:** 844, 1950.

[10] Iseri, L. T., Alexander, L. C., McCaughey, R. S., Boyle, A. J., and Myers, G. B.: Water and electrolyte content of cardiac and skeletal muscle in heart failure and myocardial infarction. Am. Heart J. **43:** 215, 1952.

[11] Harrison, T. R., Pilcher, C., and Ewing, G.: Studies in congestive heart failure. IV. Potassium content of skeletal and cardiac muscle. J. Clin. Invest. **8:** 325, 1930.

[12] Cort, J. H., and Matthews, H. L.: Potassium deficiency in congestive heart failure: Three cases with hyponatremia including results of potassium replacement in one case. Lancet **1:** 1202, 1954.

[13] Aikawa, J. K.: Unpublished data.

[14] Lesser, G. T., Dunning, M. F., Epstein, F. H., and Berger, E. Y.: Mercurial diuresis in edematous individuals. Circulation **5:** 85, 1952.

[15] Aikawa, J. K., and Fitz, R. H.: Alterations in exchangeable sodium content, "sodium^{24} space" and body weight during the treatment of congestive failure. Circulation **12:** 897, 1955.

Experiences with Pulsus Alternans

Ventricular Alternation and the Stage of Heart Failure

By J. M. Ryan, M.D., J. F. Schieve, M.D., H. B. Hull, M.D., and B. M. Oser, M.D.

Three years' experience with pulsus alternans, including its production with exercise, has shown that alternans may exhibit at least 3 types of behavior, and has led the authors to believe that the type of behavior a patient presents is related to the degree of heart failure present. Those patients who developed alternans following exercise were not in cardiac failure clinically, and yet hemodynamic data indicated myocardial insufficiency. A sustained pulsus alternans at rest seems to have no special prognostic significance in heart failure.

THREE years' experience with pulsus alternans has suggested a correlation between the circumstances under which this phenomenon is present and the degree of myocardial insufficiency. The purpose of this communication is twofold: To develop this concept and to question the grave prognostic significance usually accorded to alternans.

Methods and Materials

The arterial pulse, obtained directly through an arterial needle with a strain-gage manometer, was recorded simultaneously with the electrocardiogram. Control observations were made in the recumbent position, and the subject was tilted to the vertical position for 10 to 15 min. Venous tourniquets were applied for 5 to 6 min. Exercise was carried out in the recumbent position and consisted of alternate flexion and extension of the legs for 5 to 10 min.

Pulsus alternans was produced in 4 patients by exercise. The resting and exercise pulse curves of 3 patients are shown in figure 1. The first patient, F. S., was a 31-year-old white man with rheumatic aortic insufficiency who had never had cardiac failure clinically and was not being treated for it. The second patient, G.N., was a 52-year-old white man with coronary disease who had been in moderate heart failure, but had made an excellent response to treatment and was entirely asymptomatic at the time of the study, although he was receiving a maintenance dosage of digitalis. The third patient, W.S., was a 38-year-old white man with rheumatic aortic insufficiency who had been treated successfully with penicillin for subacute bacterial endocarditis due to *Staphylococcus aureus*. He too was not in apparent heart failure when the alternans was produced and was receiving no treatment.

The fourth person in whom an alternans was brought out by exercise is of special interest. This patient, C.M., was a 62-year-old white man with syphilitic aortic insufficiency, and alternation was produced on 2 separate occasions approximately 10 months apart. He had not been in cardiac failure when these 2 observations were made. Quite significant was the clinical course during the 1-year period following the second observation, and the difference in the behavior of the alternans when a third observation was made. During this interval he had developed paroxysmal nocturnal dyspnea and had taken digitalis intermittently. His heart size had increased as can be seen in figure 2. This third study showed that he then had a small but definite alternans at rest, which was slightly increased following tilting for 15 min. and virtually disappeared after 3 min. of exercise. Representative pulse curves from the second and third observations are shown in figure 3.

Results

In all patients who had a sustained pulsus alternans at rest this phenomenon was exaggerated after tilting or venous tourniquets and was diminished with exercise and passive leg raising. This observation was made in 8 individuals and is similar to the experience of Friedman, Dailey, and Sheffield.[1] Included in this group were the following types of heart diseases: hypertensive, coronary artery disease, rheumatic aortic insufficiency, and syphilitic aortic insufficiency. All these patients were, or had been, in heart failure clinically. An example is shown in figure 4.

As has been reported previously in 3 patients, the alternans virtually disappeared as con-

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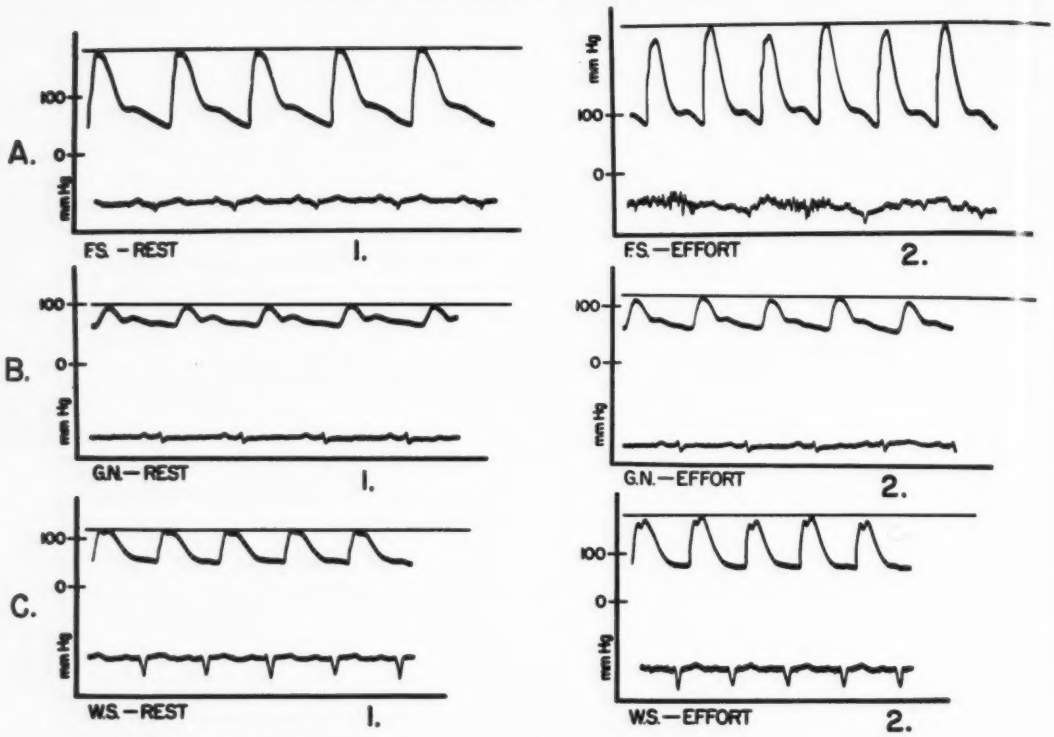

FIG. 1. *A*. F.S., a 31-year-old white man with rheumatic heart disease with aortic insufficiency. *1*. Rest. *2*. After 3 min. of exercise. *B*. G.N., a 52-year-old white man with coronary artery disease. *1*. Rest. *2*. After 3 min. of exercise. *C*. W.S., a 38-year-old white man with rheumatic heart disease with aortic insufficiency, treated for subacute bacterial endocarditis. *1*. Rest. *2*. After 10 min. of exercise.

These and the following curves are reproductions of the actual arterial pulse tracings and electrocardiograms.

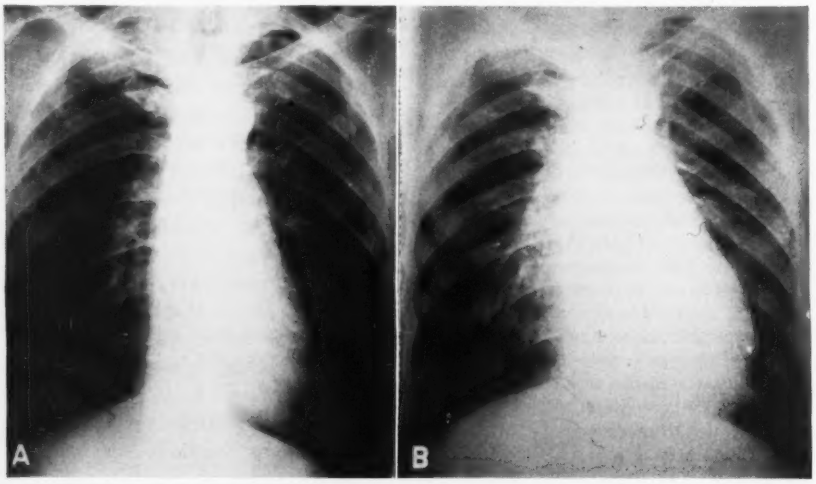

FIG. 2. Six-foot posteroanterior chest films of C.M., a 62-year-old white man with syphilitic aortic insufficiency. *A*. December 13, 1954. *B*. December 7, 1955.

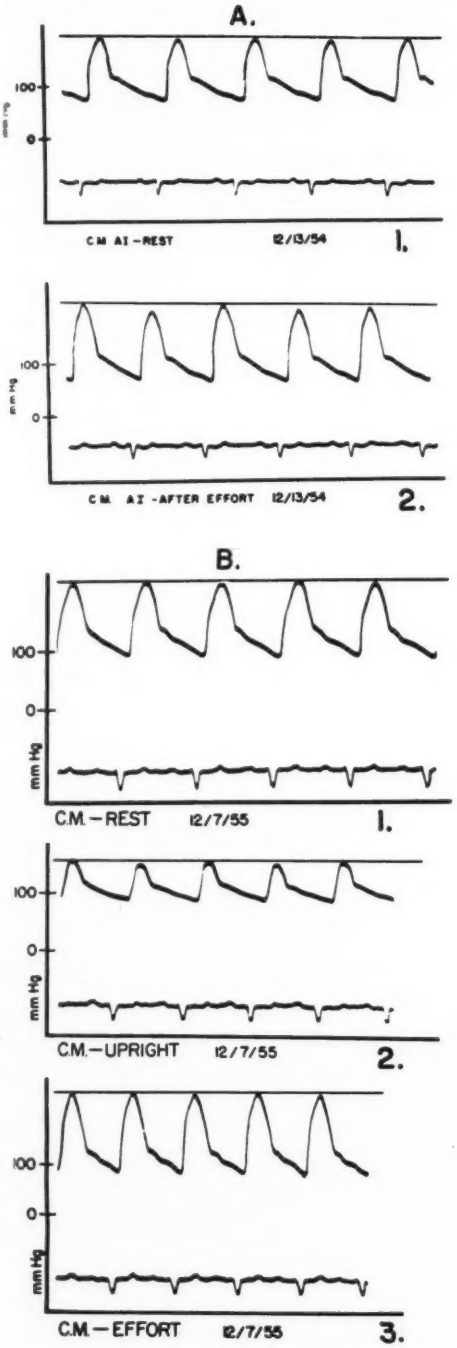

FIG. 3. C.M., a 62-year-old white man with syphilitic aortic insufficiency. *A1.* Rest on December 13, 1954. *A2.* After 3 min. of exercise on December 13, 1954. *B1.* Rest on December 7, 1955. *B2.* Upright 15 min. on December 7, 1955. *B3.* After 3 min. of exercise on December 7, 1955.

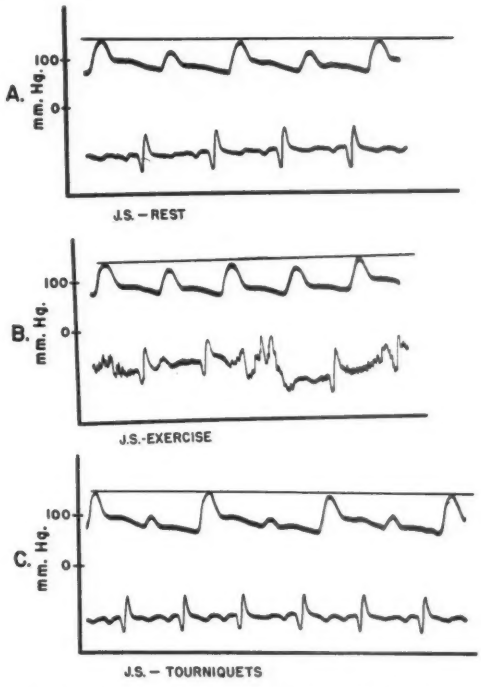

FIG. 4. J.S., a 42-year-old white man with coronary artery disease. *A.* Rest. *B.* After 5 min. of exercise. *C.* After venous tourniquets had been applied for 6 min.

gestive heart failure advanced.[2] An example is seen in figure 5.

DISCUSSION

The observations reported demonstrate that ventricular alternation can show at least 3 types of behavior, and the type exhibited seems to be dependent upon the degree of myocardial insufficiency present. The first is the appearance of alternans following exercise and may indicate myocardial insufficiency, although the patient does not have other clinical evidence of cardiac failure. Support for this concept is gained not only from our observations, but also from those of others. Cardiac catheterization showed patient W.S. to be in moderate cardiac failure at rest, as evidenced by elevations of pulmonary artery pressure and right atrial mean pressure (PA 46/32 mm. Hg, RA

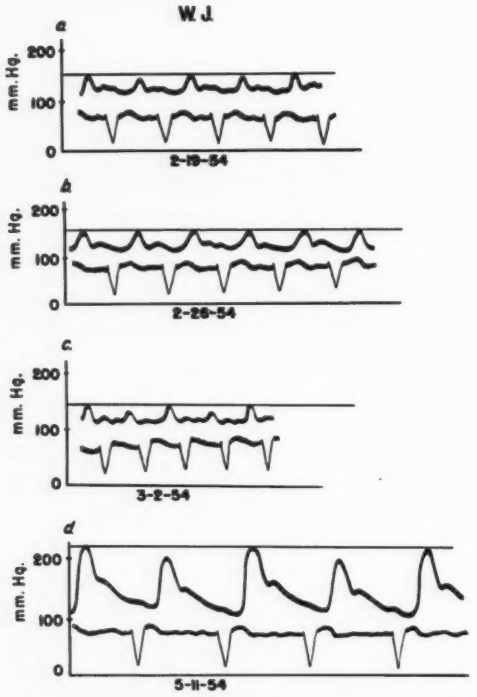

FIG. 5. W.J., a 42-year-old Negro man with hypertensive heart disease. *A*. At the time of admission; on treatment for heart failure. *B*. One week after treatment for heart failure was discontinued. *C*. Five days after treatment was restarted. *D*. Seven weeks after treatment was restarted.

11 mm. Hg). After 10 min. of exercise the pulmonary artery pressure increased to 68/46 and the right ventricular enddiastolic pressure was 16, indicating a greater degree of failure at the time the alternans appeared. Sancetta[3] noted that both a systemic and pulmonary artery alternans developed as exercise further increased the moderately elevated resting right ventricular enddiastolic and pulmonary artery pressures of a patient with rheumatic aortic stenosis. This patient showed no clinical evidence of cardiac failure at the time of study. Ferrer and associates[4] encountered a systemic pulsus alternans as exercise caused a moderate increase in the normal resting pulmonary artery pressure of a patient with hypertensive heart disease. Heart failure also was not clinically apparent in the individual.

The second type of behavior is sustained alternans at rest, which is exaggerated by a decreased venous return to the heart, such as following venous tourniquets and vertical tilting, and is diminished when the return is increased as by exercise or passive leg raising. We have not encountered an alternans at rest that did not react in this fashion. Patients with this type were either in or had been in clinical heart failure.

The third type, as previously reported,[2] is alternans that disappears as congestive failure becomes more severe. Three such patients have been encountered. Thus, alternation can disappear even though cardiac function is deteriorating.

It is known that in certain patients, digitalis may cause pulsus alternans to disappear.[1, 5] As a rule, these patients do not have a severe degree of cardiac failure; since myocardial efficiency is increased by the effect of digitalis, cardiac function may be improved to such an extent that alternation disappears. Digitalis may also have a direct effect upon myocardial factors that permit alternation; thus, improved cardiac function might not be the sole explanation for the disappearance of alternans following digitalis.

As left heart catheterization becomes more widely used, it might be found that for a given heart, pulsus alternans occurs only over a critical range of ventricular filling pressure.

Excluding the type that normally occurs for the first 2 or 3 beats following a premature contraction, the authors have not encountered pulsus alternans in the absence of organic heart disease. Therefore, although the actual reasons for its inception and perpetuation are unknown, we believe myocardial factors peculiar to certain diseased hearts are necessary for the production of alternation.

Our experience indicates that a patient with a sustained alternans at rest has just as good a prognosis as one without alternans, but with a similar type of heart disease and degree of failure. This view is at variance with the prognostic implication usually ascribed to this phenomenon.[6] On the other hand, if pulsus alternans is absent at rest, but can be pro

duced by exercise, it may indicate myocardial insufficiency in an asymptomatic patient, and thus be of prognostic importance. Further observation, however, is necessary to substantiate this last point.

If our concept is correct, that there may be a relationship between the state of myocardial insufficiency and the type of behavior an alternans exhibits, it would seem theoretically possible for a single patient to manifest each of the 3 patterns of alternation as he progresses from an asymptomatic state to an advanced stage of heart failure. Although we have not observed all 3 in 1 individual, it appears that patient C.M. has shown 2 different types. First, when asymptomatic, the alternans was present only after exercise and later, as his disease progressed, it was apparent after tilting, but absent after exercise.

Summary

Three different types of behavior of pulsus alternans have been observed. The type a patient shows may be related to the degree of heart failure present. Pulsus alternans has been produced by exercise when it was absent at rest. Although this occurred in patients who showed little clinical evidence of cardiac failure, it may be indicative of myocardial insufficiency. A sustained alternans at rest seems to have no special prognostic significances.

Summario in Interlingua

Ha essite observate tres distincte typos de comportamento de pulso alternante. Le typo de pulso alternante manifeste in un certe patiente es possibilemente relationate al grado de su disfallimento cardiac. Pulso alternante ha essite producite per exercitio in casos in que illo esseva absente in stato de reposo. Ben que le patientes in question exhibiva pauc signos de disfallimento cardiac, le phenomeno es possibilemente un indication de insufficientia myocardial. Un sustenite pulso alternante in stato de reposo ha apparentemente nulle special signification prognostic.

REFERENCES

1. Friedman, B., Daily, W. M., and Sheffield, R. S.: Orthostatic factors in pulsus alternans. Circulation **8:** 864, 1953.
2. Ryan, J. M., Schieve, J. F., Hull, H. B., and Oser, B. M.: The influence of advanced congestive heart failure on pulsus alternans. Circulation **12:** 60, 1955.
3. Sancetta, S. M.: Diastolic overload in mechanical ventricular alternans. J. Lab. & Clin. Med. **46:** 342, 1955.
4. Ferrer, M. I., Harvey, R. M., Cournand, A., and Richards, D. W.: Circulatory studies in pulsus alternans of the systemic and pulmonary circulations. Circulation **14:** 163, 1956.
5. Windle, J. D.: Clinical observations on the effect of digitalis in heart disease with pulsus alternans. Quart. J. Med. **10:** 274, 1917.
6. Levine, S. A.: Clinical Heart Disease. Philadelphia, W. B. Saunders Co., 1952.

I have three personal ideals. One, to do the day's work well and not to bother about to-morrow. The second ideal has been to act the Golden Rule, as far as in me lay, toward my professional brethren and toward the patients committed to my care. And the third has been to cultivate such a measure of equanimity as would enable me to bear success with humility, the affection of my friends without pride, and to be ready when the day of sorrow and grief came to meet it with the courage befitting a man.—Sir William Osler, Farewell Dinner, May 2, 1905.

Effect of Carotid Sinus Stimulation on the Electrocardiograms of Clinically Normal Individuals

By G. H. HEIDORN, M.D., AND A. P. MCNAMARA, M.D.

The cardioinhibitory effects of carotid sinus stimulation were studied by electrocardiographic means in 40 clinically normal, adult males. Although the carotid sinus reflex is of clinical importance, the measure of its effects in normal individuals is little known. Electrocardiographic changes were varied and occurred in nearly all. Almost one fourth of the patients developed ventricular asystole, and symptoms were induced in another fourth. The wide range of effects emphasizes the importance of this reflex even in normal persons and underscores the need for rigid criteria in the diagnosis of the hypersensitive carotid sinus syndrome.

THE clinical importance of the carotid sinus reflex is increasing. The hypersensitive carotid sinus syndrome is a well-recognized entity and is a frequent and important element in the differential diagnosis of syncope. Also, the carotid sinus reflex has been therapeutically applied in such diverse states as disorders of the heart beat, angina pectoris, shock, and pulmonary edema. It has been stated that a "hyperactive" response to carotid sinus stimulation is sufficient evidence to suspect underlying heart disease.

Despite this clinical significance, little is known concerning the effects of carotid sinus stimulation in individuals who are normal by clinical standards. It is the purpose of this report to present the findings obtained in a study of the cardioinhibitory effects of the carotid sinus reflex in clinically normal subjects. No observations on the vasodepressor or cerebral forms of this reflex were made.

METHODS AND MATERIALS

Forty active, clinically normal men ranging in age from 25 to 58 years (average age 39.3 years) seen during the course of a routine annual physical examination were studied. A complete history and physical examination, including an electrocardiogram and fundoscopic visualization, was done. Particular emphasis was placed on past or present evidence of syncope or lightheadedness, cardiovascular, renal, gastrointestinal, and pulmonary disease, and neck pathology. No one was receiving medication. An initial blood pressure reading below 150/90 was required.

Subjects with even minor deviations from the above requirements were excluded from the study; the strict criteria serve to explain the relative youth of the accepted group. None of the patients was overly fatigued, although emotional tensions produced by the nature of the study could not be modified.[1, 2] It is, of course, realized that coronary artery disease may be concealed from clinical view in these asymptomatic individuals. They may, however, be considered and labeled as clinically normal.

Carotid sinus stimulation followed a routine 12-lead electrocardiogram. Lead II was continuously recorded in the period preceding, during, and after stimulation. The patient was in the sitting position. The bulb of the carotid sinus was first located on the right side and stimulated by pressure and mild massage for a timed period of 30 sec. If a significant response was not obtained, multiple areas were stimulated in order to eliminate anatomic variants as much as possible. A similar procedure was followed on the left. The sitting position was chosen because it is the usual position of clinical testing, although the supine position increases electrocardiographic abnormalities.[3]

TERMINOLOGY

A definition of terms follows. It was necessary to devise this terminology to facilitate the discussion and tabulation of results.

Asystole: The absence of ventricular contraction for more than 2 sec.

Sino-atrial arrest (SAA): This term is used when asystole resulted from a failure of impulse formation in the sino-atrial node. The 2 sec

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TABLE 1.—*The Effect of Right Carotid Sinus Massage on the Electrocardiogram*

Patient number	Figure	Age	Asystole			SAB	SAS	Rate/min.		ACD	AVCD	AVCS	P-R interval		Duration of effect (sec.)†	Symptoms
			SAA	AVB	Duration (sec.)			before	during*				before	during		
1	—	43					+	92	70						6	0
2	—	36		+	3.4	+		90	—	+	+		0.17	0.22	22	0
3	—	43						75	70						0	0
4	—	55				+		75	46						18	0
5	—	42					+	100	70						9	0
6	—	46					+	98	63						14	0
7	2	51	+		4.9			70	—	+		+	0.16	0.20	30	+
8	—	53	+		4.3			62	—	+					14	0
9	—	37						100	95						0	0
10	—	42					+	97	60	+					6	0
11	—	31						80	95						0	0
12	8	58				+		55	35	+					14	0
13	5	38	+		2.5			76	—				0.14	0.10	30	+
14	7	29					+	85	69	+					9	0
15	—	37					+	64	52						11	0
16	—	39		+	2.0		+	94	—	+	+		0.15	0.27	30	+
17	—	36					+	80	57	+					10	0
18	—	36					+	76	52	+					9	0
19	—	38					+	88	72	+					8	0
20	—	48					+	92	82						10	0
21	—	31					+	102	72						5	0
22	4	43				+		80	44		+		0.18	0.30	15	0
23	—	28					+	84	70						6	0
24	—	46				+		72	49		+		0.15	0.21	9	+
25	—	37					+	90	77						7	0
26	—	42					+	82	64						6	0
27	—	34					+	76	54	+			0.16	0.12	30	0
28	—	37				+		72	40	+					16	+
29	—	37					+	78	66						9	0
30	—	47					+	95	57						17	0
31	—	34					+	85	59	+					8	0
32	—	48					+	73	52						19	0
33	—	38					+	89	66						11	0
34	—	25					+	94	74						7	0
35	—	39					+	102	62	+					30	0
36	—	25					+	78	52	+					30	+
37	6	27					+	95	66	+		+	0.16	0.18	30	0
38	9	31				+		90	40	+	+		0.15	0.23	30	+
39	—	45					+	70	58						8	0
40	1	41	+		5.7			85	—	+					24	+

SAA—Sino-atrial arrest
AVB—Atrioventricular block
SAB—Sino-atrial bradycardia
SAS—Sino-atrial slowing
ACD—Atrial conduction defect
AVCD—Atrioventricular conduction defect
AVCS—Atrioventricular conduction slowing
* Lowest rate observed.
†Time required for the electrocardiogram to return to prestimulation values.

time requirement for asystole was selected because the sino-atrial node rarely discharges at a rate of less than 30/min. under physiologic conditions. Therefore, absence of contraction for more than 2 sec. would most likely be unphysiologic in cause.

Sino-atrial bradycardia (SAB): A sino-atrial node discharge rate of 30 to 50 times/min.

Sino-atrial slowing (SAS): All other slowings of sino-atrial rate upon carotid sinus stimulation.

Atrial conduction defect (ACD): Decrease in

TABLE 2.—*The Effect of Left Carotid Sinus Massage on the Electrocardiogram*

Patient number	Figure	Age	Asystole			SAB	SAS	Rate/min.		ACD	AVCD	AVCS	P-R interval		Duration of Effect (sec.)†	Symptoms
			SAA	AVB	Duration (sec.)			before	during*				before	during		
1	—	43						82	78						0	0
2	—	36				+		75	46	+					8	0
3	—	43						70	69						0	0
4	—	55					+	76	57						18	0
5	—	42					+	95	80						12	0
6	—	46					+	90	66						9	0
7	—	51					+	75	57						8	0
8	—	53						56	56						0	0
9	—	37						98	95						0	0
10	—	42	+		2.0			97	—	+	+		0.16	0.44	9	+
11	—	31						100	100						0	0
12	—	58				+		55	45	+					6	0
13	—	38				+		75	38						30	0
14	—	29						77	72						0	0
15	—	37						70	62						0	0
16	—	39				+		92	45	+					30	+
17	—	36					+	72	59						8	0
18	—	36					+	75	52	+					9	0
19	—	38					+	87	76						9	0
20	—	48					+	85	54	+					13	0
21	—	31						80	80						0	0
22	—	43		+	2.7	+		75	—		+		0.16	0.26	10	0
23	—	28					+	86	65	+					10	+
24	—	46					+	74	54						9	0
25	—	37					+	82	75						5	0
26	—	42					+	92	75						7	0
27	—	34						60	58						0	0
28	—	37				+		85	49	+		+	0.14	0.19	30	0
29	—	37					+	76	68						8	0
30	—	47					+	82	64						13	0
31	—	34					+	80	57						30	0
32	—	48					+	74	61						8	0
33	3	38		+	2.4	+		86	—		+		0.14	0.26	19	0
34	—	25					+	95	58			+	0.14	0.19	9	0
35	—	39					+	98	80						4	0
36	—	25					+	80	57	+					30	0
37	—	27					+	95	74	+					30	0
38	—	31					+	86	54	+					30	0
39	—	45					+	85	57	+					22	0
40	—	41					+	84	64						7	0

See table 1 for key to abbreviations.

* Lowest rate observed.

† Time required for the electrocardiogram to return to prestimulation values.

amplitude or deformity of the P wave as a result of carotid sinus stimulation.

Atrioventricular block (AVB): A P wave without a ventricular response.

Atrioventricular conduction defect (AVCD): When the P-R interval is lengthened more than 0.21 sec.

Atrioventricular conduction slowing (AVCS): When the P-R interval is lengthened upon carotid sinus stimulation, but not more than 0.21 sec.

RESULTS

Electrocardiographic Findings. Ventricular asystole varying in duration from 2 to 5.7 sec was present in 9 of the 40 individuals studied

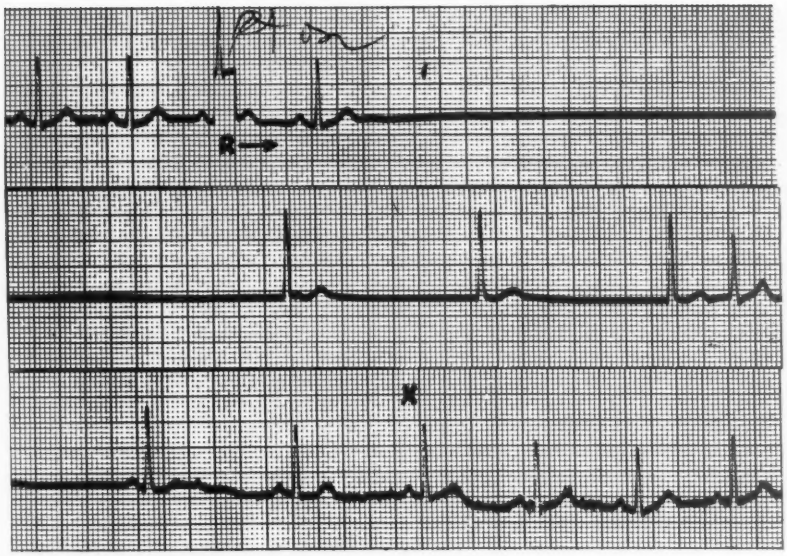

FIG. 1. Patient no. 40 illustrates a 5.7 sec. period of asystole due to sino-atrial arrest. Atrioventricular nodal escape resulted, the only time it was observed in this study. Syncope and generalized muscular twitching occurred at *X*.

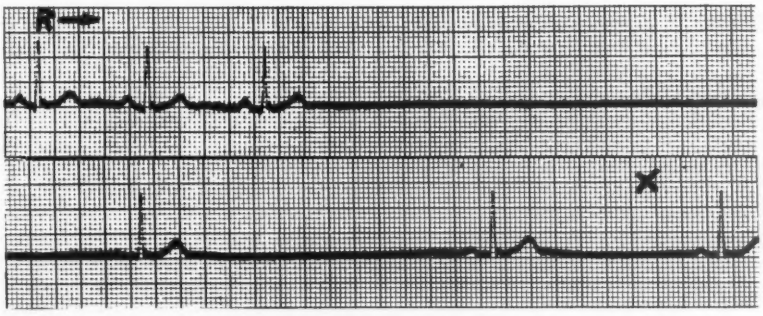

FIG. 2. Patient no. 7 illustrates sino-atrial arrest and sino-atrial escape with a 4.9 sec. period of asystole. Decreased P wave amplitude (ACD) and an atrioventricular node conduction slowing (AVCS) are also present. Moderate lightheadedness began at *X* and lasted for 5 to 10 sec.

(tables 1 and 2). The mechanism was sino-atrial arrest (figs. 1 and 2) 4 times from the right and once from the left side, and atrioventricular block (fig. 3) twice from each side. No patient developed asystole on both right and left-sided massage.

Sino-atrial bradycardia (figs. 2–5) was induced in 7 patients on right-sided and in 7 on left-sided carotid sinus stimulation. The P-R interval was significantly lengthened (fig. 4) 7 times on the right and 5 times on left-sided massage. Interestingly, the P-R interval was shortened (fig. 5) twice upon right carotid sinus stimulation.

Changes in the P wave were the most interesting of the electrocardiographic findings. A decrease in P-wave amplitude or a disappearance of the P wave was produced 18 times on the right and 12 times on the left side (figs. 6 and 7). Disappearance of the P wave (figs. 6 and 8) does not imply cessation of atrial activity. The uninterrupted rhythmicity of the heart beat in these illustrations supports the belief that the pacemaker remains in the

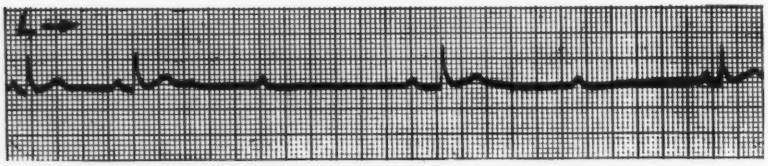

FIG. 3. Patient no. 33 demonstrated a 2.4 sec. interval of asystole due to atrioventricular nodal block upon left carotid sinus stimulation. Sino-atrial bradycardia and an atrioventricular conduction defect other than the episodes of block were also present. No symptoms were experienced.

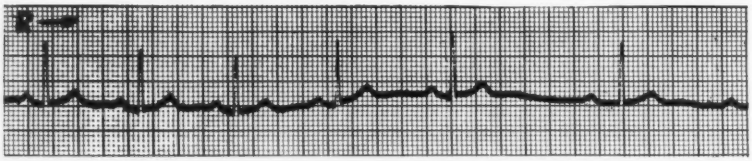

FIG. 4. Patient no. 22 showed sino-atrial bradycardia with a sino-atrial rate of 46/min. An atrioventricular conduction defect is also present. The P-R interval is increased from 0.18 sec. before stimulation to 0.30 sec. during stimulation. The patient was asymptomatic.

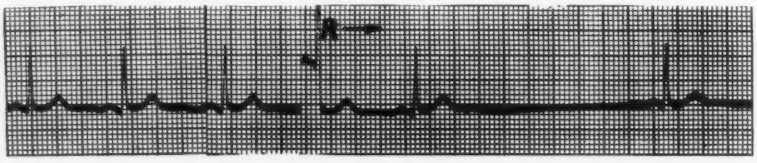

FIG. 5. Patient no. 13 developed a shortening of the P-R interval from 0.14 to 0.10 sec. upon right carotid sinus stimulation.

atrium. The atrial pacemaker probably shifts from its usual location in the sino-atrial node. Other electrocardiographic leads or other graphic methods might illustrate this shift. A definite shift of the pacemaker from the atrium to the atrioventricular node (atrioventricular nodal escape following sino-atrial arrest) occurred only once (fig. 1). The decrease in P-wave amplitude, recorded more often than P-wave disappearance, is probably the reflection of a lesser shift in the location of the pacemaker. The possibility that these P-wave changes are a reflection of qualitative or quantitative variations in electric conduction over the usual pathways without shifts of pacemaker must also be considered.

A shortening of the P-R interval following carotid sinus stimulation (fig. 5) was recorded on 2 occasions. The duration of the P-R interval is primarily a reflection of the time required for the electric impulse to pass through the atrioventricular node. Therefore, the shortening of this interval during the period of stimulation may be due to an increased speed of conduction through the atrioventricular node. However, this change may also again be explained by a shift of the atrial pacemaker toward the atrioventricular node.

A "paradoxical P-wave effect" followed carotid sinus stimulation in 1 subject (fig. 8). It is termed "paradoxical" because the changes recorded were the reverse of those usually encountered or expected. Stimulation of the right carotid sinus caused disappearance of the P wave in the recorded lead. The P wave returned to prestimulation levels while the right sinus was still being massaged. After right-sided stimulation was stopped the P waves disappeared "spontaneously." They did not return until the left carotid sinus was stimulated. These effects, although "paradoxical," are in all probability another demonstration of shifts of the atrial pacemaker.

It must be mentioned that there is a striking

absence of effects on ventricular muscle (QRS and T-wave changes) following carotid sinus stimulation in these individuals. This fact is to be expected from the known anatomic demonstration that vagal fibers are sparse in the ventricular muscle. No instance of indirect ventricular effect, such as ventricular escape from sino-atrial arrest or atrioventricular block, was recorded. On one occasion a single ventricular premature systole was noted during right carotid stimulation (patient no. 20). Also, on one occasion ST-segment elevation resulted from right carotid sinus massage (fig. 6).

Symptoms. Symptoms induced by carotid sinus stimulation varied considerably and had no correlation with the electrocardiographic changes produced (table 3). Ten patients (25 per cent) had definitive symptoms. Only one developed symptoms on both right and left carotid sinus pressure. Ventricular asystole

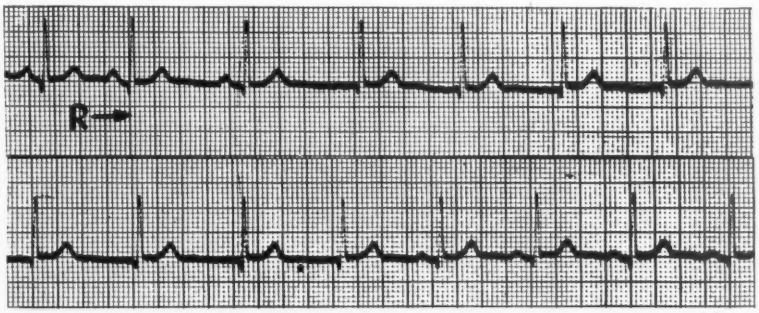

FIG. 6. This tracing of patient no. 37 illustrates disappearance of the P wave with return at a reduced amplitude during right carotid sinus stimulation. There is also slight but definite elevation of S-T segments during the period of stimulation. This patient was asymptomatic.

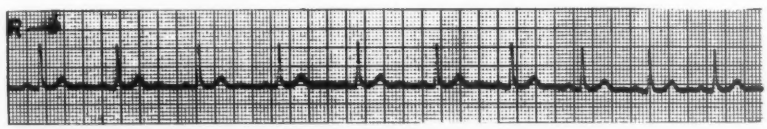

FIG. 7. Patient no. 14 showed a moderate reduction of P-wave amplitude. Any decrease in the amplitude of P waves of lesser degree than illustrated in this tracing was not recorded in the results.

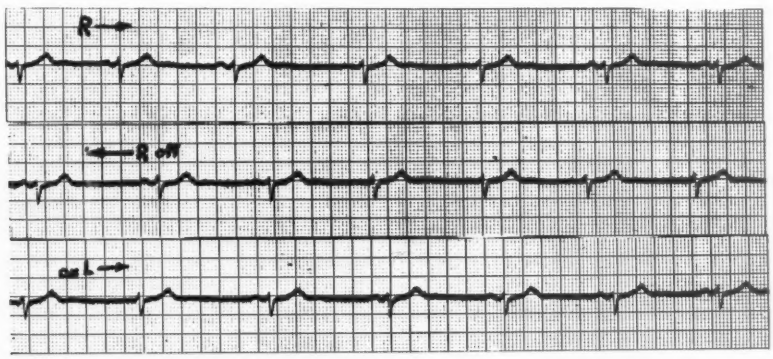

FIG. 8. Patient no. 12 revealed the only example of a "paradoxical P wave effect" recorded in this study. Several seconds of this tracing between the second and third strip are not illustrated. No symptoms were experienced.

TABLE 3.—*Tabulation of Symptoms Induced by Carotid Sinus Stimulation*

Patient number	Age	Carotid sinus	Symptoms	Principal electrocardiographic changes
7	51	R	Moderate lightheadedness	Sino-atrial arrest for 4.9 sec.
10	42	L	Moderate lightheadedness, brief syncope; numbness, muscle twitches in the right leg and foot.	Sino-atrial arrest for 2.0 sec., partial AV nodal block.
13	38	R	Numbness and tingling in the left hand	Sino-atrial arrest for 2.5 sec.
16	39	R	Minor lightheadedness in the first 10 sec.	AV nodal block resulting in 2.0 sec. of asystole.
16	39	L	Minor lightheadedness in the last 10 sec.	Sino-atrial bradycardia.
23	28	L	Moderate lightheadedness in the last 10 sec.	Sino-atrial slowing.
24	46	R	Moderate lightheadedness began after 15 sec.	Sino-atrial bradycardia.
28	37	R	Minor lightheadedness at the onset	Sino-atrial bradycardia.
36	25	R	Severe nausea began after 20 sec.	Sino-atrial slowing in the last 10 sec.
38	31	R	Severe nausea and lightheadedness after 15 sec.	Sino-atrial bradycardia in the last 10 sec.
40	41	R	Severe lightheadedness, syncope, and generalized muscle twitches after 10 sec.	Sino-atrial arrest for 5.7 sec.

was present in those with symptoms 5 times; but asystole was not associated with symptoms on 4 other occasions. It must be restated in the light of these findings that only the cardioinhibitory type of the carotid sinus reflex was studied. The cerebral and vasodepressor forms may have been operative in producing symptoms in those patients with only minor electrocardiographic changes. Indeed, they may also have been the major or entire factor in some of the subjects with symptoms who did have more marked electrocardiographic effects.

A detailed discussion of the symptoms produced by the carotid sinus reflex is not planned and can be found elsewhere.[4-10] Nausea as a symptom, however, deserves some added mention. It occurred in 2 patients. The major electrocardiographic changes in both were present in the last half of the 30-sec. period of stimulation (fig. 9). It is possible that these electrocardiographic changes were not a direct demonstration of the carotid sinus reflex, but were secondary to increased vagotonia due to gastrointestinal changes. The time lag observed before changes occurred suggests this explanation.

DISCUSSION

This study was undertaken in order to formulate some standard of normalcy that could be used in the evaluation of the hypersensitive carotid sinus syndrome and as a point of departure in the study of the therapeutic applications of this reflex in various disorders of the heart beat,[9, 11] pulmonary edema,[12] shock,[13] and angina pectoris.[14, 15] Observations in clinically normal individuals have been surprisingly sparse in the past.[16, 17]

It must be emphasized that the carotid sinus reflex is of considerable importance also in the clinically normal individual. Stimulation of the sinus resulted in ventricular asystole in 9 of the 40 patients studied. It caused clear clinical symptoms in 10 patients (25 per cent). Indeed, in only 3 patients was no electrocardiographic response obtained upon either right or left-sided stimulation.

This study serves to strengthen the clinical belief that the diagnosis of a hypersensitive carotid sinus syndrome should be made only when the symptoms experienced during attacks are reproduced *exactly* by clinical stimulation. Changes noted on the electrocardiogram, even to the point of asystole, are insufficient evidence, as this finding is often present normally.

The observation that the carotid sinus reflex is more sensitive or of greater magnitude in patients with arteriosclerotic cardiovascular disease, especially coronary artery disease, has

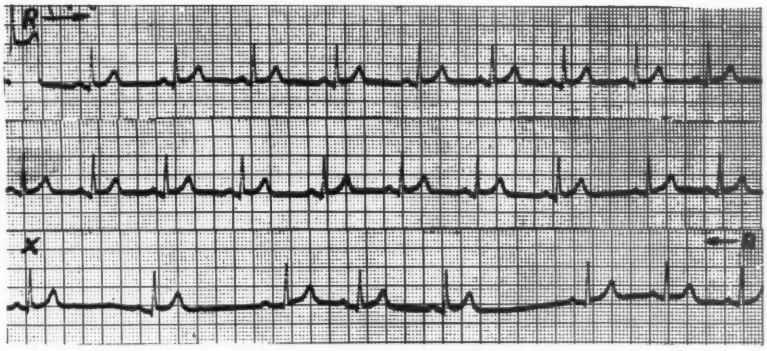

FIG. 9. This tracing illustrates the electrocardiographic effects in patient no. 38, who experienced severe nausea during sinus stimulation. Nausea occurred at *X*. Patient no. 36 had similar findings.

been previously made.[4,6,18-20] This is probably a sound clinical impression. However, it has also been stated that a marked response from carotid sinus stimulation is an indication of underlying cardiac disease.[20, 21] Our study suggests that this opinion must be accepted with considerable reservation, as marked responses occur in the clinically normal individual. A 10- or 20-year follow-up of the positive reactors in this study in relation to the development of cardiac disease would be of interest.

It would appear from a review of the literature that the dominant member in the carotid sinus reflex has been the right carotid sinus. This has also been true in this study. The left carotid sinus, however, is not to be ignored. It produced the major effect in 9 patients, one fourth of all patients in whom a response was obtained. Likewise, there was no specific localization of effect from either carotid sinus upon the sino-atrial or atrioventricular node. While the right vagus nerve supplies the sino-atrial node primarily, and the left vagus is concentrated on the atrioventricular node, a bilateral vagal supply to all supraventricular areas is known to exist. There may be a bilateral central nervous system representation as well. In this study, both carotid sinuses produced generally similar qualitative effects.

In conclusion, it must be stated that in the study of carotid sinus reflex effects, a standardization of technic in stimulation must be used. It is difficult to state the exact amount of pressure and massage used by each investigator. However, the time interval of stimulation can be controlled; we have arbitrarily chosen a 30 sec. period. Electrocardiographic effects or symptoms were often obtained only after stimulation of 10 to 15 sec. duration. We were also impressed by the occasional occurrence of little or no reflex effects upon the first site of stimulation in the anatomic location of the carotid bulb and, at times, on a palpable bulb. If multiple sites of stimulation were tried with a short rest interval between, only 3 individuals in this series did not show some significant effect.

SUMMARY

Forty clinically normal, active, adult men were studied for electrocardiographic changes induced by carotid sinus stimulation.

The results include a wide variety of electrocardiographic changes and induced symptoms. These findings emphasize the importance of this reflex, even in the apparently normal individual.

This report supports the clinical observation that the criteria for the diagnosis of the hyperactive carotid sinus syndrome must be kept within the rigid bounds of an *exact* reproduction of symptoms upon diagnostic carotid sinus stimulation. Electrocardiographic changes or the production of other symptoms is insufficient evidence to establish this diagnosis, as

such changes are often present in the individual who is normal by clinical standards.

The opinion that a "hyperactive" response indicates underlying cardiac disease has been reported in several publications. This study suggests that this opinion should be accepted with much reservation.

The purpose of this report is to establish some knowledge of what is within the range of normal. Normal standards have been neglected in past reports. A standard technic of carotid sinus stimulation and a nomenclature to be used in tabulating results are suggested for use in further studies of the carotid sinus reflex.

ACKNOWLEDGMENT

The assistance of Mrs. Helen Jordan, R.N., Mrs. Helen Botteicher, R.N., and Mrs. Alvina Trotta is gratefully acknowledged.

SUMMARIO IN INTERLINGUA

Quaranta clinicamente normal, active adultos mascule esseva studiate relative al alterationes electrocardiographic inducite per stimulation del sino carotic.

Le resultatos include un grande varietate de alterationes electrocardiographic e symptomas inducite. Iste constatationes sublinea le importantia de iste reflexo, mesmo in le apparentemente normal individuo.

Le presente reporto supporta le observation clinic que le criterios pro le diagnose del syndrome de hyperactivitate del sino carotic debe esser tenite intra le confinios rigide de un *exacte* reproduction del symptomas post stimulation diagnostic del sino carotic. Alterationes electrocardiographic o le production de altere symptomas non suffice como evidentia in establir le diagnose, proque tal alterationes es frequentemente trovate in individuos que es normal secundo le standards clinic.

Le opinion que un responsa "hyperactive" indica un subjacente morbo cardiac ha essite exprimite in varie publicationes. Le presente studio suggere que ille opinion non pote esser acceptate sin grande reservationes.

Le objectivo del presente reporto es delinear lo que es intra le limites del norma. In le passato, multe reportos ha negligite le standards de lo que es normal. Es proponite un technica standard pro le stimulation del sino carotic e un nomenclatura pro uso in tabular resultatos de futur studios del reflexo del sino carotic.

REFERENCES

[1] WEISS, S., CAPPS, R. B., FERRIS, E. B., JR., AND MUNRO, D.: Syncope and convulsions due to hyperactive carotid sinus reflex: Diagnosis and treatment. Arch. Int. Med. **58:** 407, 1936.

[2] EVANS, E.: The carotid sinus. J.A.M.A. **149:** 1, 1952.

[3] SCHERF, D., AND DIX, J. H.: Effects of posture on AV conduction. Am. Heart J. **43:** 494, 1952.

[4] WEISS, S., AND BAKER, J. P.: The carotid sinus reflex in health and disease. Medicine **12:** 297, 1933.

[5] SIGLER, L. H.: Clinical observations on the carotid sinus reflex. The response to carotid sinus pressure at various ages, heart rates, and rhythms. Am. J. M. Sc. **186:** 118, 1933.

[6] NATHANSON, M. H.: Hyperactive cardioinhibitory carotid sinus reflex. Arch. Int. Med. **77:** 1, 1946.

[7] BURNS, E. M.: Carotid sinus syndrome. Northwest Med. **53:** 247, 1954.

[8] KENNEDY, F., AND OSBORNE, R. L.: The role of the carotid sinus in blood pressure control: A review of its anatomy, physiology, pharmacology, and clinical consequences. M. Clin. North America **33:** 619, 1949.

[9] TANNEY, A. D., AND LILIENFELD, A.: The cardiovascular aspects of carotid sinus hypersensitivity with special reference to some cardiac arrhythmias. Ann. Int. Med. **16:** 676, 1942.

[10] STERN, J. E.: Abdominal manifestations of the hyperactive carotid sinus reflex. J.A.M.A. **110:** 1986, 1938.

[11] BELLET, S.: Clinical Disorders of the Heart Beat. Philadelphia, Lea and Febiger, 1953.

[12] ALZAMORA-CASTRO, V., BATTILANA, G., GARRIDO-LECCA, G., RUBIO, C., ABUGATTAS, R., AND BOURONCLE, J.: Acute left ventricular failure and carotid sinus stimulation. J.A.M.A. **157:** 226, 1955.

[13] LUZUY, M., AND TROUVE, J.: Anesthetic infiltration of the carotid sinus in the treatment of collapse and in the prevention of operative shock. Mém. Acad. chir. **72:** 74, 1946.

[14] FREEDBERG, A. S., AND RISEMAN, J. E. F.: Observations on the carotid sinus reflex and angina pectoris. Circulation **7:** 58, 1953.

[15] LEVINE, S. A., AND HARVEY, W. P.: Temporary relief of anginal pain by carotid sinus stimulation. Tr. A. Am. Physicians **60:** 225, 1947.

[16] PURKS, W. K.: Electrocardiographic findings fol-

lowing carotid sinus stimulation. Ann. Int. Med. **13:** 270, 1939.

[7] SIGLER, L. H.: Electrocardiographic observations on the carotid sinus reflex. Am. Heart J. **9:** 782, 1934.

[8] WENCKEBACH, K. F., AND WINTERBERG, H.: Die unregelmässige Herztätigkeit. Leipzig, Wilhelm Engelmann, 1927.

[19] BRAUN, L., AND SAMET, B.: "Vagusdruck" und Koronärgefäss. Deutsch. Arch. klin. Med. **161:** 251, 1928.

[20] DRAPER, A. J.: Cardioinhibitory carotid sinus syndrome. Ann. Int. Med. **32:** 700, 1950.

[21] PEARSON, R. J., AND MACGREGOR, J. B.: Cardioinhibitory effects of carotid sinus pressure. J. Florida M. A. **34:** 416, 1952.

Corcoran, A. C., Dustan, H. P., and Page, I. H.: The Evaluation of Antihypertensive Procedures, with Particular Reference to Their Effects on Blood Pressure. Ann. Int. Med. **43:** 1161 (Dec.), 1955.

Evaluation of antihypertensive drugs and procedures involves observations that are more easily correlated in a single graphic chart than in the conventional hospital records. The data can also be conveniently summarized in a numerical "severity index." The datum selected for the index as representative of arterial pressure cannot be based on casual readings of blood pressure. These average about 20/10 mm. Hg higher than the corresponding week's means of readings made twice daily, either by nurses in the hospital or by the patient or his family at home. This difference between casual readings and weekly means of readings is not diminished by treatment with hydralazine or reserpine, and is widely variable. Means of pressures measured in hospital, on the other hand, are representative, in that they center in the range of the week's series of readings and, when grouped together, correspond on the average to clinical estimates of the patients' status. In successive weeks, these means tend to stabilize after 1 week in most patients, so that the mean of the second or third week is usually a satisfactory base-point for evaluation of an antihypertensive drug. Means of home readings are considered equally representative with means of hospital readings, to which they commonly correspond. Differences between home and hospital means, when they occur, demonstrate the necessity of maintaining like conditions during a therapeutic study and usually have a satisfactory explanation. Home means show a very narrow range of variation from week to week and, in general, provide highly reproducible data. The inadvisability of home readings of blood pressure has been urged on the assumption that the making of these will create a neurotic obsession. A review of data from patients taking home readings does not show an increased incidence of psychiatric disability as compared with patients who are not making home readings, although several of the patients developed depressive reactions during the course of the observation. The depressions in these patients had apparently preceded the taking of home pressures, and became manifest either with the passage of time and release of some restraint or during medication with reserpine. Hence, although the taking of home pressures is not considered either necessary or desirable in the majority of patients, it was not found to be really psychologically disadvantageous and, in some patients, proved useful and reassuring to the patient while at the same time it provided the therapist with reliable data. The recording of weekly means of pressures, measured either in hospital or at home, is recommended as part of a program of evaluation of antihypertensive procedures.

WENDKOS

The Heart and Electrocardiogram of an Alligator

By L. Minor Blackford, M.D.

The phylogenetic evolution of the cardiovascular system of animals and man has been a subject of continued interest. The reported study of the cardiovascular system and electrocardiogram of the alligator bears on this subject. The author has cogently remarked that this journal, which has reported similar studies in the beluga whale, should be the vehicle of his report.—Ed.

Spitzer[1] in 1923 was not the first to point out the similarity of certain anomalies of the human heart to hearts that are normal lower in the evolutionary ladder. He remains however one of the staunchest proponents of the theory that "The phylogenetic cause [of congenital heart disease] is an arrest of development at a lower phylogenetic level, related to but not identical with that of reptiles, and the coordination of the features of this stage with those already developed in the mammalian stage." The heart of the crocodile, with an aorta arising from each ventricle, in addition to a pulmonary trunk from the right ventricle, particularly impressed him. The anomaly called by different authors "dextroposition of the aorta," "überreitende Aorta," and "riding aorta" Spitzer explained as "a fusion of both [right and left] aortas extending from the proximal bulbus to the ventricle."

Accepting this thesis, in 1932[2] we suggested "biventricular aorta" as a term readily understandable, one phylogenetically and anatomically correct, and one that would simplify terminology by the elimination of eponyms. If this term were accepted, "Eisenmenger complex"[3] would be supplanted by "biventricular aorta," and the condition commonly known in this country as "the tetralogy of Fallot"[4] would be "biventricular aorta with pulmonic stenosis."

In 1935 a case in a 19-year old boy in which both ventricles sent blood into the aorta, without pulmonary stenosis, and other cases in which the aorta arose from both ventricles with pulmonary stenosis or atresia, aroused my interest in the heart of the *Crocodilia*. An alligator about 75 cm. long was therefore secured from Jacksonville for study.

Taking an electrocardiogram on a live alligator is not without difficulties. It was necessary to muzzle the reptile and then to anesthetize it with ether. Electrodes applied to the hide caused no deflections. Pins were then inserted into the forelimbs and into the left hindlimb, and these were connected with the electrodes.

That warm October afternoon the rate was 50. Probably on a cold day without ether or in a state of hibernation, the rate would have been slower. In lead I no deflections were observed; today this might be best explained on the basis of a vertical electric axis. No tracing in this lead was preserved. In leads II and III, low deflections were noted (fig. 1). As in the case of the beluga whale,[5] the P waves were not very distinct, but it was thought that the P-R interval was 0.28 sec. The R wave in lead II measured 2.5 mm. In lead III the R was slightly lower and rather slurred. The T waves were also poorly defined in both leads.

Later, again under ether, the ventral wall of the alligator was sectioned. The heart was located about midway between the forelimbs and the hindlimbs. It was interesting to watch it slowly beating. In systole the myocardium was almost white, overlaid with tiny, cyanotic coronary vessels; in diastole the whole heart was dark blue-red. This indicated that the circulation through the heart muscle beneath the epicardium was carried on essentially during the resting period. It also indicated that

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Presented before the Fulton County Medical Society, August 2, 1956.

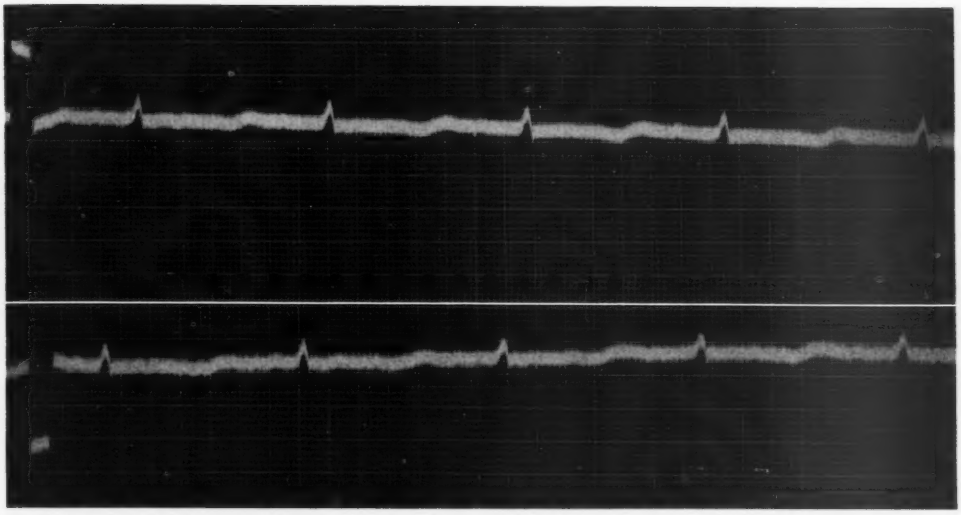

FIG. 1. The electrocardiogram of the alligator, taken October 15, 1935. The rate is 50. Lead I showed no deflections and was not preserved. Though the P waves are not very distinct, the P-R interval is 0.28 sec. The R waves are low and slurred. The T waves are also indistinct.

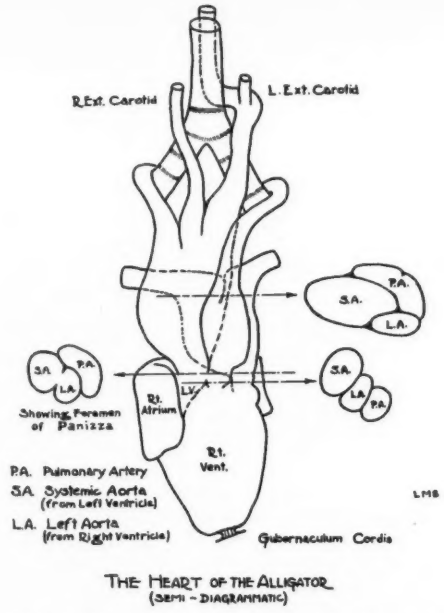

FIG. 2. The heart of the alligator with cross sections of the great vessels, showing the foramen of Panizza. The aorta arising from the left ventricle and arching over the right bronchus is continued caudad as the systemic aorta. Just above its origin it communicates with the aorta from the right ventricle, a small continuation of which loops over the left bronchus. Back of the heart this descending limb of the aorta from the right ventricle joins again the systemic aorta.

there was considerable mixing of venous blood from the right ventricle with the freshly oxygenated blood from the left ventricle through the foramen of Panizza.

The heart continued to beat after being placed in saline. The laboratory grew cold that fall night and in the morning the heart was still. Further dissection showed that the wall of the right ventricle was about as thick as that of the left, as might be expected, for it has to sustain a pressure equal to that from the left ventricle. No attempt had been made to determine the pressure in the great vessels, nor have I encountered any blood pressure determinations in an alligator. Though pulmonary hypertension had unquestionably been present, the pulmonary arteries were not examined for arteriosclerotic changes, nor for hypertrophy of the muscularis. Because so little has been written in the last 30 years about the cardiovascular system of the *Crocodilia*, and because what little has been written is not readily available to clinicians, a drawing of the alligator's heart is presented (fig. 2).

While at first blush it might seem remarkable that an alligator can get along so well with such a low degree of oxygen tension (and legend says that some live to be 100, though with the present commercial demand for alligator skins few specimens in excess of 18 feet are found), it must be remembered that fish, turtles, and frogs, all poikilothermic animals like the alligator, live active lives with probably even less oxygen. Moreover, White and Sprague[6] have reported the case of a composer who completed a distinguished career in his sixtieth year, though deeply cyanotic his life long.

Summary

Because of the intense interest in congenital heart disease today and because of the accumulating electrocardiograms of the whale, it seems appropriate now to present the electrocardiogram of a Florida alligator done in 1935.

Acknowledgment

The help of the late Dr. Edgar D. Shanks in taking the electrocardiogram and of Dr. John H. Venable in dissecting the alligator is gratefully acknowledged.

Addendum

On September 12, 1956, an opportunity was afforded me to take another electrocardiogram on a 64-inch alligator from the Atlanta Zoo. It was a cool day, temperature 70, and cooler the night before. With the aid of 3 attendants, the reptile was not anesthetized, and it remained fairly quiet. The rate was 35; otherwise it was essentially like the first tracing from the smaller alligator.

Summario in Interlingua

A causa del intense interesse in congenite morbo cardiac in nostre dies e a causa del accumulante electrocardiogrammas de balenas, il pare appropriate presentar nunc le electrocardiogramma de un alligator de Florida, executate in 1935.

References

[1] Spitzer, A.: Ueber den Bauplan des normalen und missbildeten Herzens: Versuch einer phylogenetischen Theorie. Virchows Arch. path. Anat. **243:** 81, 1923.

[2] Blackford, L. M., Davenport, T. F., and Bayley, R. H.: Right aortic arch. I. Clinical report of a case with associated anomalies. Am. J. Dis. Child. **44:** 823, 1932.

[3] Eisenmenger, V.: Die angeborenen Defekte des Kammerschildewands des Herzens. Ztschr. klin. Med. **32:** Supplement, 1, 1897.

[4] Fallot, A.: Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque). Marseille méd. **25:** 17, 138, 207, 270, and 403, 1888.

[5] King, R. L., Jenks, J. L., Jr., and White, P. D.: The electrocardiogram of a Beluga whale. Circulation **8:** 387, 1953.

[6] White, P. D., and Sprague, H. B.: The tetralogy of Fallot: Report of a case in a noted musician who lived to his sixtieth year. J. A. M. A. **92:** 787, 1929.

Navratil, L., Wenger, R., and Kaindl, T.: On the Etiology of Congenital Heart Disease. Arch. Kreislauflorsch. **22**: 225, 1955.

One hundred mothers of children with congenital heart disease, compared to 200 mothers of normal children, showed a statistically significant higher incidence of late menarche, irregular menstruation, temporary sterility, spontaneous abortion, and a higher age at the time of labor. Coincidence of maternal and fetal hormonal insufficiency at a critical point of fetal development is considered as the probable cause of congenital heart disease.

Lepeschkin

Studies Made by Simulating Systole at Necropsy

VIII. Significance of the Pulse Pressure

By Isaac Starr, M.D.

In a previous publication we defined the relation between cardiac work and blood pressure measurements by means of multiple regression equations. In this communication we seek a simple method of estimating cardiac work from observations any doctor could make in the clinic.

LONG before blood pressure could be measured in the clinic, the nature of the relation between the amplitude of the pulse and the cardiac stroke volume was discussed. It is mentioned in a report of studies of the recorded pulse by Roy and Adami in 1890,[1] in a similar report by Mackenzie in 1902,[2] and surely the same idea must have occurred much earlier to countless imaginative doctors who, when feeling the pulse, speculated on the aspect of cardiac performance that produced the sensation they perceived through their fingers. During this era, exact knowledge of the relationship was not possible, for the amplitude of the recorded pulse varied with the pressure with which the pick-up unit was applied to the artery, and it was therefore difficult to interpret in quantitative terms.

As soon as blood pressure could be measured in the clinic, more exact knowledge was sought.[3] Thus, a direct relation between pulse pressure and cardiac stroke volume was proposed by Erlanger and Hooker in 1905.[4] Later, many attempts were made to define the relation more exactly, and several methods designed to estimate cardiac stroke volume from pulse pressure were proposed, based on the theoretic conceptions favored by the various authors at that time.[5-9] Recently, workers from this laboratory have brought forward methods of estimating stroke volume from pulse pressure, based, not on any theory, but on regression equations derived from measurements made after simulating systole in experiments on cadavers.[10]

Indeed, it seems almost self-evident that the amplitude of the pulse wave, expressed as the pulse pressure, should be somehow related to the size of the cardiac stroke volume, which is its genesis. But a relationship between the magnitude of the pulse pressure and the work performed by the heart at each stroke did not seem self-evident at all, at least to me. So, when results indicating that pulse pressure was related much more closely to stroke work than to stroke volume began to turn up in the data secured in our cadaver experiments, I was taken by surprise. But I soon discovered that, by reasoning from their theoretic conceptions, the Scandinavian school had anticipated this finding.

In 1928, Liljestrand and Zander[5] published the results of experiments supporting a very simple view of the relation between stroke volume and the blood pressure, which has been expressed as follows:

$$\textit{Stroke volume} = L \frac{\textit{pulse pressure}}{\textit{mean pressure}} \qquad (1)$$

L being a constant that was expected to vary from subject to subject. However, the validity of such a simple relationship was disputed by the German school[8, 11] whose theoretic conceptions and experimental results indicated a much more complicated relationship between stroke volume and blood pressure, dependent on many additional factors such as the elasticity and size of the vessels. At that time, the only way

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to test the validity of such ideas was to compare the blood pressure data with the results secured by the cardiac output methods then available. Since there was little knowledge of the absolute accuracy of these flow methods, it is not surprising that the results secured by one group were not always confirmed by those obtained by another. In our experiments in which systole was simulated in cadavers at necropsy,[10] the stroke volumes employed were accurately known, and the results supported the view of Liljestrand and Zander that their simple formula provided a useful approximation of stroke volume.

Twelve years later, a logical extension of Liljestrand and Zander's conception was made by Apéria[12] but, buried in an advanced mathematic treatise on the dynamic theory of the circulation, the simple conception he proposed seems to have been altogether overlooked. Apéria produced no evidence for the correctness of his view, but he clearly pointed out that, since the approximate formula for cardiac work was:

$$\textit{Cardiac work} = \textit{stroke volume} \times \textit{mean pressure} \quad (2)$$

then, by substituting from the Liljestrand and Zander equation (1), we have:

$$\textit{Cardiac work} = L\ \textit{pulse pressure}. \quad (3)$$

By this simple mathematic expression, Apéria[12] set forth the view that the pulse pressure provides a quantitative measure of changes occurring in the work of the heart of any patient. But, I know of no clinician using the pulse pressure for this purpose at the present time, although a simple method of estimating the heart's work would be welcomed by everyone.

A second feature of this conception will also take clinicians by surprise. The height of the blood pressure is an important factor in the estimation of cardiac work, but Apéria's formula indicates that pulse pressure measures the work independently of the height of the blood pressure.

The purpose of this paper is to record a test of Apéria's idea by means of the results secured by simulating systole in our cadaver experiments; for in these, curves of cardiac ejection and of both central and peripheral blood pressure had been recorded graphically, and the "left ventricular" work performed could be estimated by integration with an accuracy not approached in experiments performed on living men or mammals. Our results support the simple conceptions of the Scandinavian school in emphatic fashion. Indeed, the pulse pressure proves much more closely related to the work performed by the heart than to its output.

Material and Methods

The technic of the experiments in which systole was simulated in cadavers at necropsy has already been described in detail.[13] In brief, after raising the pressure to the diastolic level by perfusing fluid into a femoral artery, systole was simulated by injecting fluid into the root of the aorta and pulmonary artery from syringes, the injection being powered by a blow of known energy. The amount injected at every instant was recorded by an optical system. Central and peripheral blood pressures were secured by 2 optical manometers connected with small tubes, the tip of 1 lying in the root of the aorta, that of the other in the femoral artery. The ballistocardiogram was recorded also, but this paper is not concerned with that measurement.

In the series of 144 "systoles" conducted on 16 cadavers, the stroke volume, blood pressure, and the contour of the ejection curve were varied widely as we aimed to explore the ranges found clinically.[14] In some subjects, the vessels were altogether normal in appearance, in others, arteriosclerosis was advanced. The experiments themselves must be divided into 2 groups; those in which blood was used to fill the vessels and simulate systole, and those in which water was used for these purposes. The results secured in each group will be analyzed separately.

The experiments in which *blood* was used were performed at the end of our long series after our technic had been brought to its highest point. The clinical and necropsy findings on the 6 cadavers of these series have been recorded. The curves of cardiac injection at each instant of systole have been published, and the values of stroke volume, central and peripheral systolic and diastolic pressure, pulse wave velocity, etc. are also on record.[14] From the curves of cardiac injection and of central blood pressure, "left ventricular" work was calculated for me by Dr. Walter Feder,[15] by multiplying the values instant by instant and integrating the resulting curves, thus securing values for work, as work was defined by Sir Isaac Newton, which are certainly far more accurate than any that have been secured in living men or mammals. These accurate values of work, which will be designated as "true work," can be compared with the peripheral pulse pressures secured in the same "systoles." Statistical analysis has been performed

n the results secured in 51 such "systoles" in 6 adavers; that is, on all the results obtained except in which the duration of ejection was far longer han any systole to be expected during life, and 1 in hich, through an oversight, work was not measured y integration.

The experiments in which *water* was used both to ll the vessels and simulate systole, performed arlier, were not so technically perfect as the experients in which blood was used, and the various easons for this have been discussed. Technical leficiencies made us discard all the results secured n several experiments. Most of these were lost beause of the difficulty inherent in photographic reording; errors of technic that ruined the records nd were not recognized until the film was developed t the end of the experiment. All the results secured n 2 other cadavers were disregarded for reasons of a lifferent kind. In 1, the brain, of great interest to he pathologist, was removed before our experiments egan, in the fear that our injections of water might distort the pathologic picture by creating edema; so he common carotid and innominate arteries were tied before reasonable diastolic pressures could be secured, greatly reducing the vascular bed. In another early experiment, a mediastinal tumor so distorted the anatomy that the rigid glass cannulas used at the time had to be forced into their usual position in the aorta and pulmonary artery; distortions were produced thereby that might well have kinked the vessels. While it seemed wise to omit all data secured from these last 2 subjects, they could have been included without damage to any of our conclusions.

After thus omitting all data from 5 subjects, we still had satisfactory data from 93 "systoles" secured in 10 other cadavers perfused by water, and this seemed a sample of ample size. Except for the omissions noted above, this sample includes all the results secured after the technic had been improved by powering the injections mechanically by a swinging mallet, in place of pushing in the syringe plungers by hand.

Because the different physical properties of water and blood made the results of the "water" experiments less clearly applicable to conditions existing during life, the labor of estimating "cardiac" work by integration was not undertaken in this group. We contented ourselves by calculating work without regard to time by formula (2), which we have shown to give a reasonably good estimate of the true work.[18] The results of such estimates will be called "approximate work."

The clinical diagnosis and autopsy findings of most of the cases perfused with water have already been published.[13-15] However, in this communication additional data will be used from 4 other subjects not previously described. The essential clinical data and necropsy findings of these were as follows:

Subject 24. V.S., a man of 49, 75 Kg. weight and 174 cm. tall, died of acute lymphatic leukemia. At necropsy, the heart showed subacute bacterial endocarditis of mitral and aortic valves in addition to widespread findings characteristic of leukemia. The aorta and arteries were normal.

Subject 25. L.E., a man of 54, 78 Kg. weight and 170 cm. tall, had formerly been hugely obese, once weighing 135 Kg. He had been in congestive failure repeatedly without any obvious clinical explanation. Necropsy showed old myocardial infarction and coronary atherosclerosis. The aorta showed severe atherosclerosis with numerous yellow plaques, many of which were calcified and ulcerated.

Subject 26. F.C., a woman of 64, 52 Kg. weight and 165 cm. tall, died of carcinoma of the ovary with widespread metastasis. There was moderate atherosclerosis of the aorta without calcification.

Subject 27. R. P., a woman of 49, 60 Kg. weight and 166 cm. tall, after suffering from diabetes mellitus and hypertension for many years, died of renal involvement and terminal uremia. Two toes had been amputated for peripheral vascular disease. Necropsy showed renal nephrosclerosis. The aorta showed only moderate atherosclerosis, little more than would be expected for her age. There was some calcification below the bifurcation, but none above.

Results and Discussion

The relations between pulse pressure and stroke volume, and pulse pressure and true "left ventricular" work, secured in subjects perfused with *blood* are shown in figures 1–3, and the regression equations have been placed in tables 1 and 3. Similar relations for the subjects perfused with *water* are shown in figures 4–6 and in tables 2 and 4. In these tables, the regression equations have been numbered serially with those of our preceding communications derived from data secured in our cadaver experiments. The multiple regression equations recorded in tables 3–5 were calculated for me by Dr. Albert Schild.

In the statistical analysis of our data, the results secured on subjects perfused with blood have not been combined with those secured on subjects perfused with water, because the great differences in viscosity between water and blood made it unlikely that similar quantitative relations would be found for the 2 series. This was borne out by the results, for certain significant differences were found, and they will be mentioned before the much greater similarities will be discussed. Thus, the slopes of the comparable regressions in figures 1 and 4, equations

TABLE 1.—*Regression Equations from Data Secured in Fifty-one Simulated Systoles Performed in Six Cadavers Perfused by* Blood *Relating Stroke Volume and True "Left Ventricular" Work to Peripheral Pulse Pressure; and Such Work to Mean Peripheral Blood Pressure*

Equation Number	Equation	σ	Correlation coefficient
94	Stroke Volume *ml.* = 35.9 + 0.21 pulse pressure *mm. Hg*	13.45 *ml.*	0.40
95	True Work *Gm. M.* = 1.1 + 1.13 pulse pressure *mm. Hg*	18.3 *Gm. M.*	0.86
96	True Work *Gm. M.* = 0.54 + 68.4 $\frac{\text{pulse pressure } mm.\ Hg}{\text{age } years}$	16.6 *Gm. M.*	0.89
97	True Work *Gm. M.* = −8.0 + 0.78 mean blood pressure *mm. Hg*	26.2 *Gm. M.*	0.69

TABLE 2.—*Regression Equations from Data Secured in Ninty-three Simulated Systoles Performed in Cadavers Perfused with* Water *Relating Stroke Volume and Approximate "Left Ventricular" Work to Peripheral Pulse Pressure*

Equation Number	Equation	σ	Correlation coefficient
98	Stroke Volume *ml.* = 32.1 + 0.21 pulse pressure *mm. Hg*	12.9 *ml.*	0.47
99	Approx. Work *Gm. M.* = 25.2 + 0.59 pulse pressure *mm. Hg*	17.1 *Gm. M.*	0.74
100	Approx. Work *Gm. M.* = 18.6 + 44.8 $\frac{\text{pulse pressure } mm.\ Hg}{\text{age } years}$	15.3 *Gm. M.*	0.80

95 and 99, are significantly different ($t = 4.67$). In the experiments in which blood was employed, a given increase in pulse pressure represents a greater increase in work. This difference would be expected from the more viscous nature of blood, which causes greater loss of energy in friction during its passage to the periphery. Also, in the data from "blood" experiments, the regressions of pulse pressure with both work, and work divided by age, pass very close to the origin indeed; in the data secured in the corresponding water experiments they pass somewhat farther away. Despite these differences, the results of the 2 sets of experiments confirm each other in surprising fashion as far as their main features are concerned, as will now be set forth.

Pulse Pressure and Stroke Volume

A glance at figures 1 and 5 shows that this relationship is a poor one: the regressions pass far from the origin and the scatter is large. If one divides figure 1 by a line from the origin to the opposite corner, all the points fall to the right of and below this line and they are scattered quite evenly throughout this triangular area. The points in figure 5 show a similar distribution.

From this distribution of the data, several deductions of general interest to clinicians can be pointed out. If peripheral pulse pressure is unduly large, it is safe to believe that stroke volume is abnormally increased. But if this pulse pressure is small, no deduction about the

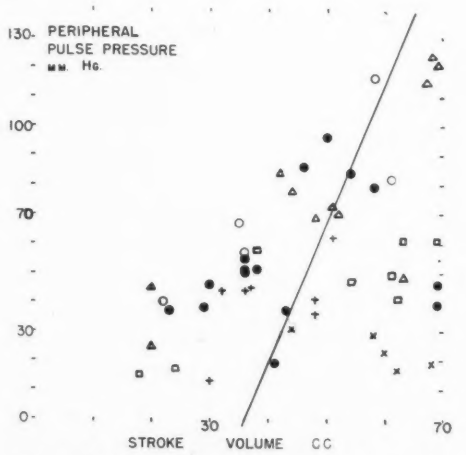

FIG. 1. Relation between *peripheral pulse pressure* and *stroke volume*. Data from 6 subjects perfused with *blood*. The data secured on the different subjects are represented as follows: for M.L., squares; H.Z., triangles; P.L., circles; R.R., dots; J.W., crosses; M.M., x's. The solid line is the calculated best line for the group corresponding with regression equation 94 of table 1. r = 0.40.

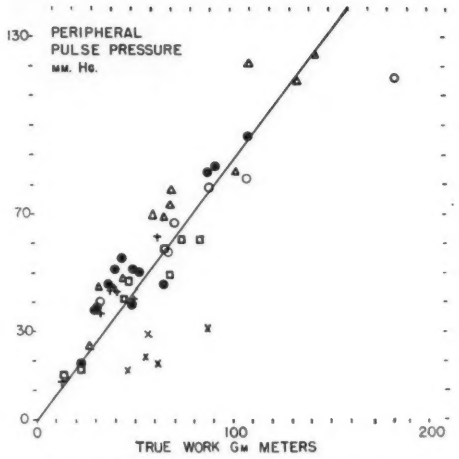

FIG. 2. Relation between *peripheral pulse pressure* and *true stroke work*. Data from 6 subjects perfused with *blood*; symbols as in figure 1. The solid line is the calculated best line of the group and it corresponds to regression equation 95 of table 1. r = 0.86.

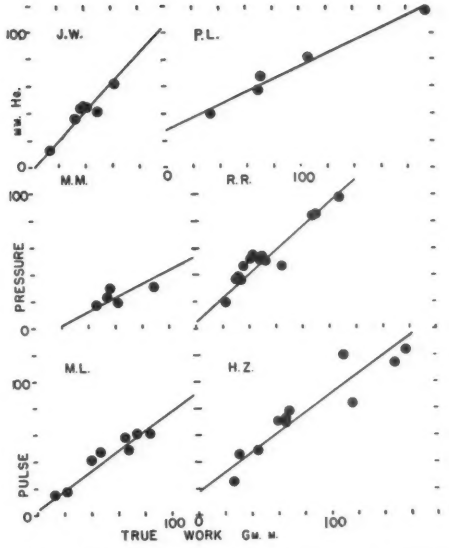

FIG. 3. Relation between *peripheral pulse pressure* and *true stroke work* in each of the 6 subjects perfused with *blood*. The solid lines are the regressions for each subject proper for estimating work from pulse pressure. r = : for J.W., 0.95; P.L., 0.99; M.M., 0.70; R.R., 0.94; M.L., 0.98; H.Z., 0.93.

size of the stroke volume can be safely made, for it may be either small or large. When the tension in the large arteries is low, a stroke volume of considerable size may not produce a pressure wave that reaches the periphery in the identifiable form of a pulse wave. Therefore, when the patient is pulseless, or if blood pressure cannot be secured, it does not necessarily mean that stroke volume is 0. This may well account for experiences in which patients, pulseless for considerable periods of time and believed to be dead, have revived unexpectedly. Our findings are also consistent with the observations that in conditions of syncope, when blood pressure and the pulse often cannot be secured, the circulation through an arm may still be large.[16]

Pulse Pressure and Stroke Work

Comparisons between figures 1 and 2 and between figures 4 and 5 show clearly that the relation between peripheral pulse pressure and *work* is the greatest improvement over that between pulse pressure and stroke volume. The relationship between pulse pressure and work is clearly linear and so good that it is no exaggeration to say that the pulse pressure measures the work of the left ventricle.

When the relations between pulse pressure and cardiac work are examined in individual subjects, figures 3 and 6, one sees that most of the points are surprisingly close to their regressions. The scatter around the best line of the groups taken as a whole is largely due to differences between individuals. The slopes of the regressions differ from one subject to another, but if the slopes are arranged according to the age of the subjects, it becomes evident that age is an important factor in this difference, although it may not be the whole story. Thus, in figure 3, the regressions of R.R. and J.W., the 2 oldest subjects, are the most nearly vertical, while the regressions of M.M. and M.L., the youngest, are much more nearly horizontal. Similarly in figure 6, the most upright regressions, those of E.S. and A.McG., pertain to the 2 oldest subjects, while the most horizontal, V.S. and P.L., are those of the 2 youngest subjects. The effect is that, as one grows older, a given heart work results in a larger pulse pressure. The constant "*L*" of Apéria's formula (3) is thus found to vary with age.

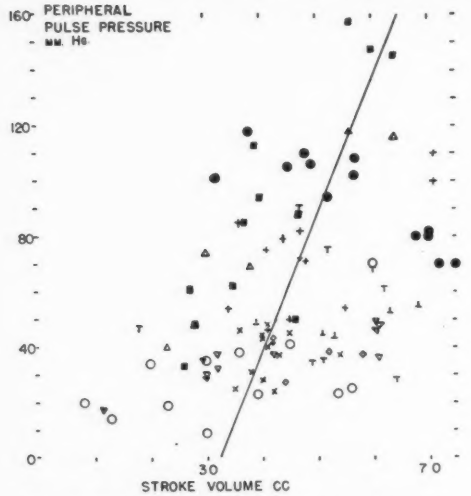

FIG. 4. Relation between *peripheral pulse pressure* and *stroke volume* in 10 cadavers perfused with *water*. The data secured on the different subjects are represented as follows: A.McG., dots; P.L., triangles with point up; E.B., circles; E. Sco., squares; J.I., crosses; E. Sch., x's; R.P., T's; F.C., diamonds; L.E., triangles with point down; V.S. inverted T's. The solid line is the calculated best line for the group, corresponding to regression equation 98 of table 2. r = 0.47.

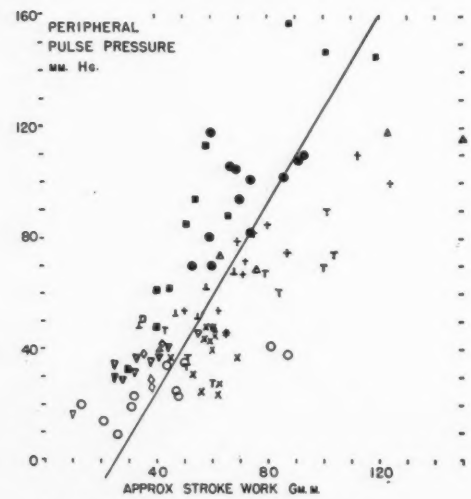

FIG. 5. Relation between *peripheral pulse pressure* and *approximate stroke work*. Data from 10 cadavers perfused with *water*; symbols as in figure 4. The solid line is the calculated best line of the group corresponding to regression equation 99 of table 2. r = 0.74.

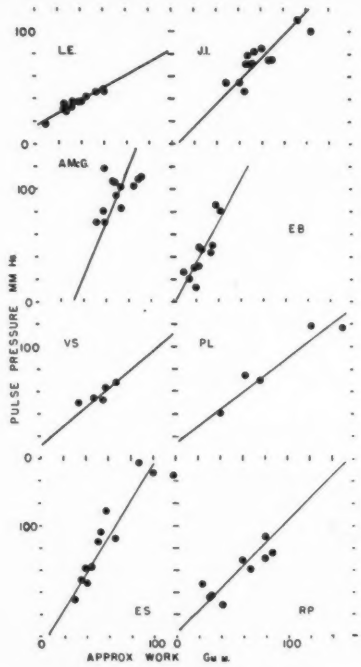

FIG. 6. Relation between *peripheral pulse pressure* and *approximate stroke work* in 8 of the 10 subjects perfused with *water*. The solid lines are the regressions for each subject proper for estimating work from pulse pressure. r = : for L.E., 0.96; J.I., 0.86; A.McG., 0.53; E.B., 0.85; V.S., 0.88; P.L., 0.95; E.Sco., 0.91; R.P., 0.87. In the 2 remaining subjects the data were so concentrated that the true slope of the regressions could not be defined with confidence.

Therefore, if one estimates left ventricular work from blood pressure, a correction for the age of the subjects will improve the results. The magnitude of the necessary correction has been investigated in 2 ways. In the first, work was compared with pulse pressure divided by age; the results are shown in figures 7 and 8, and the corresponding regression equations are in tables 1 and 2. Considerable improvement has resulted by this means, the standard deviations about the regressions diminishing by 9 and 11 per cent.

To secure maximum improvement from a consideration of the subject's age, and to see if consideration of the subject's size and the size and elasticity of his aorta would also improve estimates of heart work from pulse pressure,

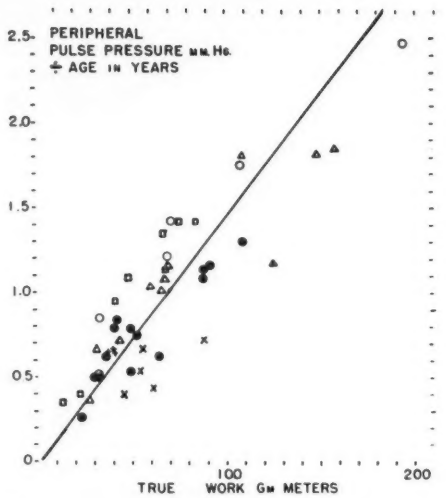

FIG. 7. Relation between *peripheral pulse pressure divided by age*, and *true work*. Data from 6 cadavers perfused with *blood*. The calculated best line corresponds to equation 96 of table 1. r = 0.89.

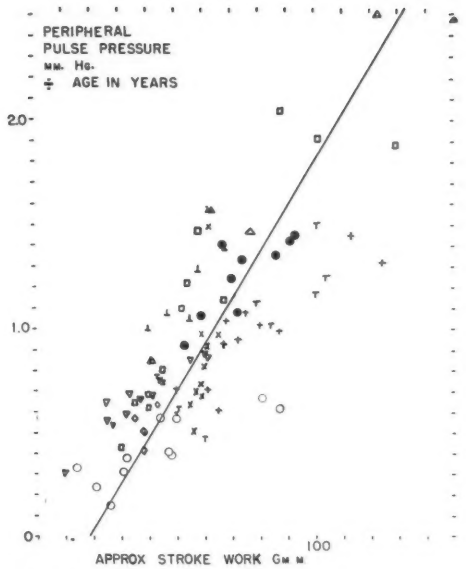

FIG. 8. Relation between *peripheral pulse pressure divided by age* and *approximate work*. Data from 10 cadavers perfused with *water*. The calculated best line corresponds to equation 100 of table 2. r = 0.80.

multiple regression equations were computed by Dr. Albert Schild (tables 3–5). In the subjects perfused with blood, the improvement in the estimate of work from pulse pressure and age, gained by using the multiple regression equation 101, is very little better than that secured by simply dividing pulse pressure by age and using the simple regression equation 96; in subjects perfused with water, there is no material gain in using the corresponding multiple regression equation 104 over the ratio equation 100. Also, the additional use of body surface area to provide a factor related to the size of the subject (equation 102), accomplished very little to improve the relationship in either series. The use of pulse wave velocity (equation 107), and the measurements of cross section area of the ascending aorta made at necropsy (equation 108), also provide little improvement, while their combination (equation 109) has a standard deviation indicating a little more scatter than when age (equation 101) is employed alone. These are interesting findings because one would have expected that advancing age affected the results by producing changes in aortic size and elasticity, and that direct measurements of size and elasticity would improve the results far more than age itself in the regression equations.

In looking over the regression equations in tables 1–5, readers may well wonder why, in our search for means to improve the simple estimates of work, we failed to include the most obvious factor, namely the height of the blood pressure itself. This factor does not appear because this aspect of the situation was studied first and the results have already been reported in a previous paper,[15] where multiple regression equations including both pulse pressure and mean blood pressure are to be found. It should be emphasized that the best of the simple regression equations given in this present paper does not provide so good an estimate of cardiac work as can be obtained from the best of the multiple regression equations published in this previous communication.[15] Thus, equation 85, an estimate of cardiac work from pulse pressure, mean pressure, diastolic pressure, and age, has a standard deviation about the regression of 14.9 Gm.M.[15] The corresponding standard deviations for equation 95, an estimate of work from pulse pressure alone, and equation 96, an

TABLE 3.—*Multiple Regression Equations, Computed by Dr. Albert Schild from Data Secured in Cadavers Perfused with* Blood, *Concerned with the Estimation of "Left Ventricular" Work from Clinical Data*

Equation Number	Equation	σ Gm. M.
101	True Work *Gm. M.* = 44.9 + 1.21 pulse pressure *mm. Hg* −0.79 age *years*	15.3
102	True Work *Gm. M.* = −51.5 + 1.13 pulse pressure *mm. Hg* +31.48 surface area $M.^2$	16.6
103	True Work *Gm. M.* = 15.5 + 1.20 P.P. *mm. Hg* −0.65 age *years* +12.9 surface area $M.^2$	15.1

TABLE 4.—*Multiple Regression Equations, Computed by Dr. Albert Schild from Data Secured in Cadavers Perfused with* Water *Concerned with the Estimation of "Left Ventricular" Work from Clinical Data*

Equation Number	Equation	σ Gm. M.
104	Approx. Work *Gm. M.* = 62.57 + 0.72 pulse pressure *mm. Hg* −0.73 age *years*	15.4
105	Approx. Work *Gm. M.* = 18.54 + 0.59 pulse pressure *mm. Hg* + 3.98 surface area $M.^2$	17.2
106	Approx. Work *Gm. M.* = 133.85 + 0.67 P.P. *mm. Hg* −0.95 age *years* −33.07 surface area $M.^2$	14.9

TABLE 5.—*Further Multiple Regression Equations, Computed by Dr. Schild from Data Secured in Cadavers Perfused with* Blood, *Concerned with Attempts to Improve the Estimation of "Left Ventricular" Work from Pulse Pressure by the Use of Data Not Readily Secured in the Clinic*

Equation Number	Equation	σ
107	True Work *Gm. M.* = 13.60 + 1.30 P.P. *mm. Hg* −3.12 pulse wave velocity *M. per sec.*	17.2 *Gm. M.*
108	True Work *Gm. M.* = 15.16 + 1.13 P.P. *mm. Hg* −2.22 aortic section $cm.^2$	16.7 *Gm. M.*
109	True Work *Gm. M.* = 29.57 + 1.31 P.P. *mm. Hg* −3.38 P.W.V. *M. per sec.* −2.35 aortic section $cm.^2$	15.4 *Gm. M.*

estimate from pulse pressure and age, are 18.3 and 16.6 Gm.M, respectively. Nevertheless, great interest lies in the fact that the difference in scatter is so small.

Our data indicate that one can make a reasonably good estimate of the work of the left ventricle from the magnitude of the peripheral pulse pressure alone. Indeed, it is a striking but altogether fortuitous fact, clearly shown in figure 2 and equation 95, that the magnitude of the pulse pressure in mm. Hg bears a remarkably close relation to the left ventricular work expressed as Gm.M.

Our data also indicate that in clinical estimations of work from pulse pressure one should expect to detect differences in the left ventricular work of a single patient better than differences between one patient and another. Doubtless, large differences of cardiac work could be detected by palpation of the pulse alone. By considering the patient's age, estimates of work from pulse pressure could be improved, as the same pulse pressure indicates less work as age advances. On the other hand, consideration of the size of the subject or the size of his aorta is not necessary, an estimate of pulse wave velocity is not necessary, and one does surprisingly well without considering the height of the blood pressure.

It is of great interest to compare the accuracy of such an estimate of cardiac work, made from the pulse pressure alone (equation 95), with the accuracy secured by estimating cardiac work from the height of the blood pressure

alone, for certainly most doctors now consider the latter to be the best simple clinical method of estimating the work of the heart. Accordingly, figure 9 shows the relation between mean

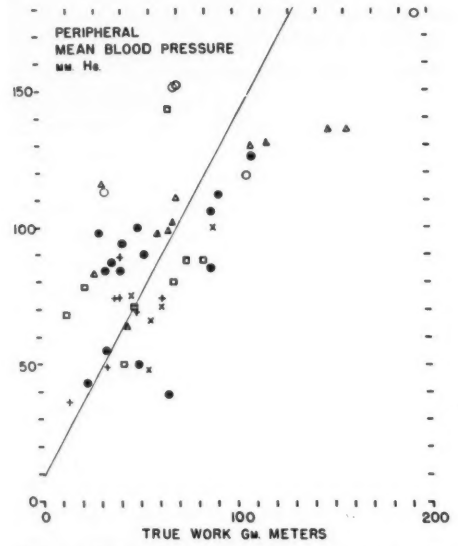

FIG. 9. Relation between *peripheral mean blood pressure* and *true work*. Data from 6 cadavers perfused with *blood*. Mean blood pressure = ⅓(systolic + diastolic pressure). The calculated best line corresponds to equation 97 of table 1. r = 0.69.

blood pressure and cardiac work as it occurs in our subjects perfused with blood, the corresponding regression equation is given as no. 97 in table 1. Comparison between figures 2 and 9 and inspection of the corresponding equations in table 1 show that the scatter about the regression is much larger with estimates of cardiac work from mean blood pressure alone than with estimates of cardiac work from the pulse pressure alone. One can make a much better estimate of cardiac work from the pulse pressure than one can from the height of the blood pressure.

I repeat that this was a surprising finding, but, on reflection, an aspect of the situation became apparent to me that went far to explain it and helped me to understand how it was possible that the pulse pressure could provide such a good estimate of the heart's work without considering the height of the blood pressure at all. Figure 10 may give more persons a better grasp of my explanation for this unexpected finding than would a detailed exposition in the text. The explanation lies in an important difference between the magnitude of the pressure changes occurring in a tense system and those occurring in a flaccid system, when fluid is injected into each.

Another analogy has helped some people to

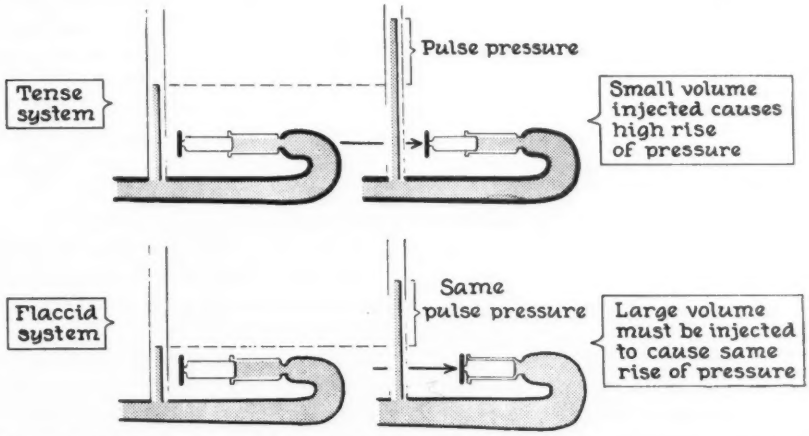

FIG. 10. A schematic diagram to illustrate the reason why the relation between heart work and pulse pressure is so largely independent of the height of the blood pressure. In the situation pictured at the top, at high pressure, WORK = Small stroke volume × large mean pressure. In the situation pictured at the bottom, at low pressure, WORK = Large stroke volume × small mean pressure. Therefore, when pulse pressures are similar WORK is quite similar, despite differences in height of blood pressure.

understand better what I have in mind. Suppose one patient has a blood pressure of 120/80 mm. Hg, another a pressure of 220/180; could their hearts be doing the same amount of work? It takes the injection of only a little fluid to produce 40 mm. pulse pressure at the higher level of blood pressure, and the work performed is roughly analogous to carrying 1 bucket of water up 2 flights of stairs; at the lower pressure level the injection of much more fluid is required to raise the pressure 40 mm., and the work performed may be likened to carrying 2 buckets of water up 1 flight of stairs.

I must emphasize that I have not said that the heart does not perform increased work in hypertension. Certainly, in a great majority of these cases, not only is the blood pressure elevated, but the pulse pressure is increased also. In such cases there is abundant evidence that heart work has increased and this is a reasonable explanation for the cardiac hypertrophy so often found. Nevertheless, cases of prolonged hypertension without cardiac enlargement are fairly common. I am hopeful that we now have a rational explanation for what appeared to be an inconsistency.

I must close as I began with some reflections on the countless doctors who, in the past, have felt the pulse of their patients to determine how the heart was "working," without attempting to employ that term in its exact sense. Although the art today is largely neglected, as a young man I recall elderly practitioners whose fingers automatically sought the wrist of any patient before them. Doubtless their spokesman was Mackenzie, who wrote,[2] "It is the strength of the left ventricle that we are gauging when we seek to determine the strength of the pulse." This view is strongly upheld by the results of this investigation.

Summary

The relationship between peripheral pulse pressure and left ventricular work, predicted by Apéria from theoretical considerations, has been explored by a statistical investigation of results secured in experiments in which systole was simulated in cadavers.

From results secured in 51 simulated systoles in 6 cadavers in which blood was used as perfusing fluid, "left ventricular" work had been estimated by integration of central blood pressure and cardiac ejection curves by Dr Walter Feder. The correlation coefficient between this "true" work and the peripheral pulse pressure was 0.86. In the same data, the correlation coefficient between stroke volume and peripheral pulse pressure was only 0.40.

In results secured in 93 simulated systoles in 10 cadavers perfused with water, "left ventricular" work was estimated approximately as the product of stroke volume and mean central blood pressure. The correlation between this work and the corresponding peripheral pulse pressure was 0.74. In the same data, the correlation between stroke volume and peripheral pulse pressure was only 0.47.

Therefore, our results demonstrate clearly that peripheral pulse pressure is much more closely related to the work performed by the left ventricle than to its stroke volume.

The relation between pulse pressure and stroke work in individuals is closer than that in groups, for the slope of the regression differs from subject to subject, being related to the age. Therefore, consideration of the age of the subject improves one's ability to estimate left ventricular work from peripheral pulse pressure. Consideration of the size of the subject, the pulse wave velocity, and the size of the aorta, leads to little additional improvement in the estimation. The use of the height of the mean peripheral blood pressure benefits the estimation much less than was expected.

The magnitude of the pulse pressure (used alone) provides a much better estimate of the left ventricular work performed than does the height of the mean blood pressure (used alone).

While the simple estimates of cardiac work from pulse pressure here described are not as accurate as are the estimates of such work made by the more elaborate equations published previously,[15] they seem accurate enough for many clinical purposes, especially for the detection of changes in cardiac work in single patients.

The data indicate that by careful consideration of the pulse pressure, or indeed perhaps simply by skillful palpation of the pulse, any clinician could detect the larger deviations in the work being performed by the left ventricle

vithout making any numerical computation vhatsoever.

Summario in Interlingua

Le relation inter peripheric pression pulsatile e labor sinistro-ventricular, predicite per Apéria ab considerationes theoric, esseva explorate per medio del investigation statistic de resultatos obtenite in experimentos in que systole esseva simulate in cadaveres.

Super le base de resultatos obtenite in 51 simulate systoles in 6 cadaveres (in que sanguine esseva usate como fluido de perfusion), le labor "sinistro-ventricular" esseva estimate per Dr. Walter Feder per medio del collation de curvas del pression de sanguine central con curvas del ejection cardiac. Le correlation de iste "ver" labor con le peripheric pression pulsatile habeva un coefficiente de 0,86. Le mesme datos monstrava un correlation inter volumine per pulso e peripheric pression pulsatile con un coefficiente de solmente 0,40.

Super le base de resultatos obtenite in 93 simulate systoles in 10 cadaveres (in que aqua esseva usate como fluido de perfusion), le labor "sinistro-ventricular" esseva estimate approximativemente como producto de volumine per pulso e pression de sanguine central medie. Le coefficiente de correlation inter iste labor e le correspondente peripheric pression pulsatile esseva 0,74. Le mesme datos monstrava un coefficiente de correlation de solmente 0,47 inter volumine per pulso e peripheric pression pulsatile.

Assi nostre resultatos demonstra clarmente que peripheric pression pulsatile es multo plus nettemente correlationate con le labor del pulso cardiac que con le volumine per pulso cardiac.

Le relation inter pression pulsatile e labor de pulso in individuos es plus stricte que in gruppos, proque le inclino del regression differe ab un subjecto al altere in relation al etate. Per consequente, le consideration del etate de un date subjecto meliora le possibilitate de estimar le labor sinistro-ventricular super le base del peripheric pression pulsatile. Le consideration del largor del subjecto, del velocitate del unda pulsatile, e del dimension del aorta adde pauco al precision del estimationes. Le uso del valor medie del peripheric pression de sanguine beneficia le estimation multo minus que lo que nos haberea expectate.

Le magnitude del pression pulsatile (usate sol) provide un multo melior estimation del labor cardiac que le valor medie del pression sanguinee (usate sol).

Ben que le simple estimationes del labor cardiac super le base del pression pulsatile (secundo le supra-describite methodo) es minus accurate que le estimationes del labor cardiac per medio del complexe computationes previemente publicate, illos pare esser satis accurate pro multe objectivos clinic, specialmente pro le detection de alterationes del labor cardiac in patientes individual.

Le datos indica que le caute consideration del pression pulsatile—o forsan mesmo solmente le habile palpation del pulso—permitte a omne clinico deteger le plus marcate deviationes in le labor del ventriculo sinistre, sin recurso a ulle computation numeric del toto.

REFERENCES

[1] Roy, C. S., and Adami, J. G.: Heart beat and pulse wave. Practitioner **44:** 81, 1890.

[2] Mackenzie, J.: The Study of the Pulse. Edinburgh and London, Young J. Pentland, 1902.

[3] Hürthle, K.: Ueber eine Methode zur Registrierung des arteriellen Blutdrucks beim Menschen. Deutsche med. Wchnschr. **22:** 574, 1896.

[4] Erlanger, J., and Hooker, D. R.: An experimental study of blood pressure and pulse pressure in man. Johns Hopkins Hosp. Reports **12:** 145, 1904.

[5] Liljestrand, G., and Zander, E.: Vergleichen die Bestimmungen des Minuten volumens des Herzens bein Menschen mittels der Stick oxydul methode und durch Blut druck messung. Ztschr. ges. exper. Med. **59:** 105, 1928.

[6] Broemser, P. H., and Ranke, O. F.: Ueber die Messung des Schlagvolumens des Herzen auf. unblutigem Weg. Ztschr. f. Biol. **90:** 467, 1930.

[7] Bazett, H. C., Cotton, F. C., Laplace, L. B., and Scott, J. C.: Calculation of the cardiac output and effective peripheral resistance from blood pressure measurements with an appendix on the size of the aorta in man. Am. J. Physiol. **113:** 312, 1935.

[8] Wetzler, K., and Böger, A.: Die Dynamik des arteriellen Systems. Ergebn. d. Physiol. **41:** 300, 1939.

[9] Remington, J. W., Noback, C. R., Hamilton, W. F., and Gold, J. J.: Volume elasticity characteristics of the human aorta and prediction of

the stroke volume from the pressure pulse. Am. J. Physiol. **153:** 298, 1948.

[10] STARR, I., SCHNABEL, T. G., JR., ASKOVITZ, S. I., AND SCHILD, A.: Studies made by simulating systole at necropsy. IV. On the relation between pulse pressure and cardiac stroke volume, leading to a clinical method of estimating cardiac output from blood pressure and age. Circulation **9:** 5, 1954.

[11] GROLLMAN, A., AND BAUMANN, H.: Schlagvolumen und Zeitvolumen des gesunden und kranken Menschen. Dresden und Leipzig, T. Steinkopff, 1935.

[12] APÉRIA. A.: Hemodynamical studies. Skandinav. Arch. f. Physiol. Supplement 16, **83:** 1940.

[13] STARR, I., SCHNABEL, T. G., JR., AND MAYOCK, R. L.: Studies made by simulating systole at necropsy. II. Experiments on the relation of cardiac and peripheral factors to the genesis of the pulse wave and the ballistocardiogram. Circulation **8:** 44, 1953.

[14] —, AND —: Studies made by simulating systole at necropsy. III. On the genesis of the systolic waves of the ballisotocardiogram. J. Clin. Invest. **33:** 10, 1954.

[15] —, ASKOVITZ, S. I., FEDER, W., AND SCHILD, A.: Studies made by simulating systole at necropsy. VII. Clinical methods for estimating the work of the left ventricle, with a note on the diminution of heart work as age advances. Circulation **12:** 1005, 1955.

[16] BARCROFT, H., AND SWAN, H. J. C.: Sympathetic Control of Human Blood Vessels. London, Edward Arnold, 1953.

Hoye, S. J., and Warren, R.: Follow-up Studies of Iliofemoral Arterial Reconstruction in Arteriosclerosis Obliterans. New England J. Med. **254:** 102 (Jan. 19), 1956.

The authors studied a group of 29 patients in whom arterial reconstruction has been performed for the treatment of arteriosclerosis obliterans involving the iliofemoral arterial trunk. Twenty-one operations were done. The follow-up period was from 2 to 29 months. Seven of the patients had associated diabetes. Only individuals with no palpable pulsations below the iliac or femoral areas but with patent popliteal arteries, as demonstrated by arteriography, were considered to be suitable candidates for the operation. Homologous arterial and autogenous venous grafts were used.

All but 3 patients left the hospital with a patent graft. Of the 16 arterial grafts, 9 closed within 7 months. Of the 13 autogenous vein grafts, 8 reoccluded, 6 within 6 months and the other 2 at 8 and 9 months.

In the 19 cases of closure, 4 limbs were improved, 9 showed no change and 6 were made worse. All of the latter came to amputation.

Twelve grafts continued to function. Seven of these were arterial and 5 were venous. Seven of the patients were followed over 6 months.

ABRAMSON

Abnormality of the U Wave and of the T-U Segment of the Electrocardiogram

The Syndrome of the Papillary Muscles

By D. Furbetta, M.D., A. Bufalari, M.D., F. Santucci, M.D., and P. Solinas, M.D.

The U wave is considered to represent repolarization of the papillary muscle and neighboring structures. In this study the various types of abnormalities in U wave and T-U segments are outlined and are related to the cardiac involvement. The common factor underlying the varied cardiac pathology is regarded to be ischemia, "strain," or other functional derangement of the papillary muscles in the right or left ventricles.

WE HAVE demonstrated[1] experimentally in dogs that the origin of the U wave is from the papillary muscles of the ventricles and probably from structures embryologically and functionally connected, such as the upper part of the interventricular septum, the interpapillary fibers, and the sphincter of the atrioventricular valves. The U wave represents repolarization of all these structures. Delay in repolarization might be caused by the circumstances under which the papillary muscles work: protracted contraction, traction along a longitudinal line, concentric compression, and probably prolonged contraction during the protodiastolic period of Wiggers. In a recent monograph we have examined all the physiopathologic arguments supporting this theory.[1]

In a review of 11,000 cases, we were able to prove clinically that every alteration of the U wave and of the T-U segment coincides with cardiovascular pathology and with definite involvement of the papillary muscles. These experimental and clinical investigations[1-11] permitted conclusions of immediate practical interest, namely, the defining of a new electrocardiographic and clinical entity: "the syndrome of the papillary muscles."

We believe that various abnormalities of the papillary muscles, whether anatomic or functional, are detectable by alterations of U waves and T-U segments. We have determined the following characteristics of this syndrome: (1) the electrocardiographic signs; (2) the pathogenesis; (3) the different types, depending on variations in site, severity, evolution, and presence of other electrocardiographic abnormalities; and (4) its incidence in various cardiovascular diseases.

From the Cardiological Center of the Institute of Clinical Medicine (directed by Prof. G. Dominici), Perugia University Medical School, Perugia, Italy.

Electrocardiographic Signs

The electrocardiographic signs of the papillary muscle syndrome consist of all the possible alterations of the U wave and of T-U segment. In figure 1 we made a schematic diagram of these alterations and also attempted to construct geometrically the corresponding vector loops. Negativity of the U wave and morphologic deformities of the T-U segment are the most significant changes and are most frequently referred to in our clinical descriptions.

Pathogenesis

Our clinical investigations supported our experimental findings and showed that U and T-U changes might be present in every cardiovascular disease where the following conditions exist: a hemodynamic situation that places a strain on papillary structures, such as a rise in intraventricular pressure, of either intracardiac or extracardiac origin; a disturbance of metabolism, as in electrolytes or proteins; or coronary insufficiency resulting in either anatomic (injury or necrosis) or functional (ischemia) abnormalities of the papillary muscles. These conditions may exist separately

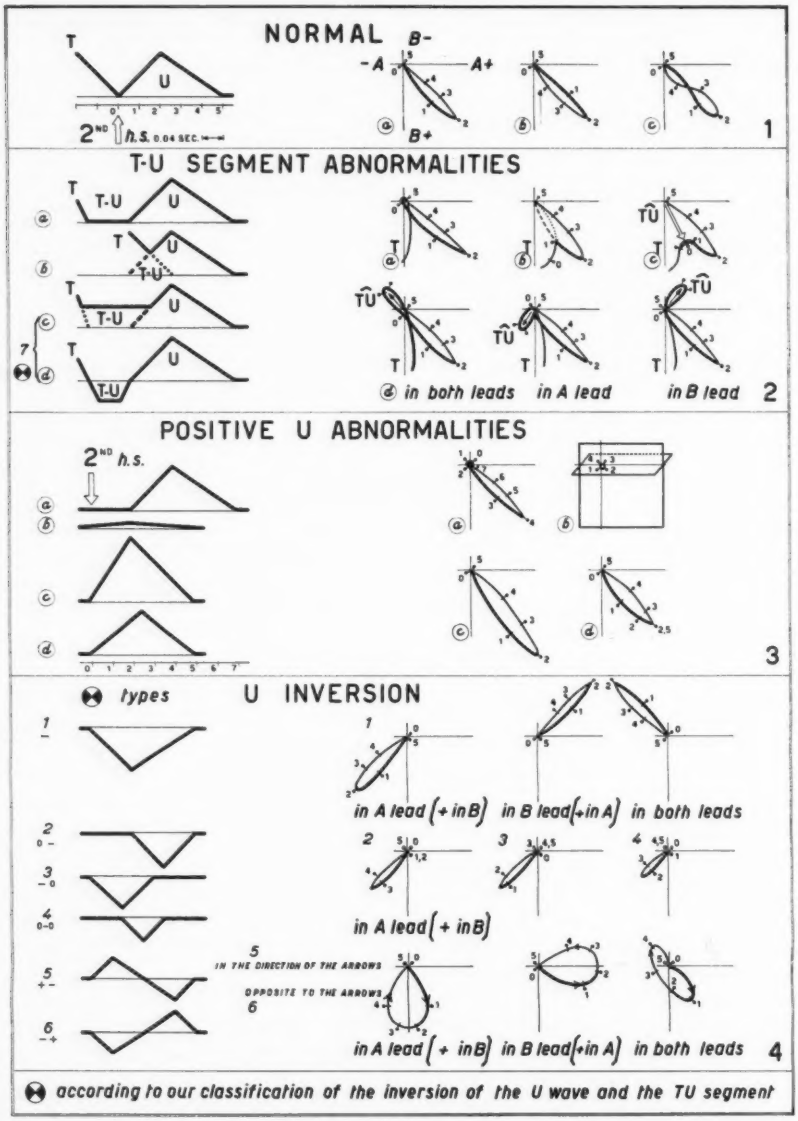

Fig. 1. Electrocardiographic and vectorcardiographic aspects of the U wave and of the T-U segment. The numbers under the electrocardiogram and on the loop indicate simultaneous points, counting from the beginning of the second heart sound with a time unit of 0.04 sec. The various vector loops refer to any 2 axes of derivation (A and B) that are perpendicular to each other and lie on any of the spatial planes (on the frontal plane leads I and V_F; on the horizontal plane, approximately, V_2 and V_6). The polarity is indicated by plus and minus signs.

1. Normal. The U wave loop may be inscribed (*a*) in a counterclockwise direction, (*b*) in a clockwise direction, and (*c*) as a "figure 8." Normally it is always projected onto the positive segments of the 2 leads (positive quadrant).

2. T-U segment abnormalities. (*a*), (*b*) chronologic, and (*c*), (*d*) morphologic (seventh type of our classification). (*a*) T-U longer than 0.04 sec.; U loop normal. (*b*) T and U confluence longer than 0.04 sec.; the final portion of the T loop is superimposed on the initial portion of the U loop. (*c*) T-U eleva-

TABLE 1.—*Most Frequent Causes of the Papillary Muscle Syndrome*

1. Extrinsic (mechanical strain)	Extracardiac	Left sided: arterial hypertension
		Right sided: chronic cor pulmonale
	Intracardiac	Left sided: aortic disease or mitral insufficiency
		Right sided: mitral stenosis, congenital heart disease with right ventricular hypertrophy
2. Intrinsic (coronary insufficiency or metabolic disturbance)	Myocardial ischemia	
	Myocardial injury or necrosis (recent or old infarct)	
	Hyperpotassemia or hypopotassemia	
	Hypoproteinemia	
3. Combined (1 + 2)	Arterial hypertension and coronary insufficiency	
	Arterial hypertension and metabolic disturbance	
	Digitalis intoxication	

or concomitantly. In table 1 we outlined the most frequent diseases that may precipitate a papillary muscle syndrome, as they occurred in our clinical investigation. Of course other diseases exist that may, by themselves or combined, affect the papillary muscles.

SITE

There are 3 different vectorial patterns of the pathologic U wave (fig. 2). Their striking correlation with sites of ventricular involvement has led to the differentiation of what might be well considered 3 types of the papillary muscle syndrome.

Left Papillary Muscle Syndrome. Negative U waves occur in leads I, aV_L, and left chest leads. The spatial U vector is directed anteriorly and to the right. Clinically, it occurs in left ventricular affections (anterior myocardial infarction, aortic and hypertensive heart disease).

Right Papillary Muscle Syndrome. Negative U waves occur in lead III, eventually in aV_F,

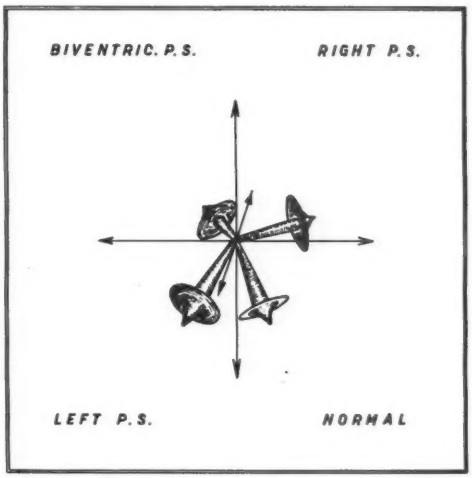

FIG. 2. Schematic representation of the orientation of the spatial U vector in the normal heart and in the papillary muscle syndrome.

tion; the T-U instantaneous vectors are inscribed in the positive quadrant of the plane. (*d*) T-U depression; the TÛ vectors are inscribed in all quadrants but the normal positive one.

3. Positive U wave abnormalities. (*a*) Delay of the U wave with respect to the second heart sound; U loop normal, but chronologically modified. (*b*) Isoelectric U wave; U loop not visible. (*c*) High voltage of the U wave; U loop correspondingly more developed. (*d*) Symmetry of the 2 branches of the U wave; equal length of the symmetrical time segments of the U loop.

4. U wave inversion. Morphologic types of negative U waves: Type 1: total inversion (−). Type 2: inversion of the initial part (−0). Type 3: inversion of the terminal part (0−). Type 4: inversion of the central part (0−0). Type 5: plus-minus diphasism (+ −). Type 6: minus-plus diphasism (− +).

Of the partially negative U wave (second, third, fourth types) we schematize only the vector aspect when present in lead A. In the fifth type the time sequence of the loop is indicated by the arrows; in type 6 it is opposite the arrows.

TABLE 2.—*Incidence of Various Types of the Papillary Muscle in the Most Common Heart Diseases*

Clinical data	No. cases	Electrocardiographic findings							Papillary syndrome							
		Normal U, T-U	Major pathology			Minor pathology			Left				Right	Biventricular	Total	
									Major			Minor				
			U	T-U	Total %	U	T-U	Total %	Pure	Combined	Total %				No.	%
Normal	100	100	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Arterial hypertension (total cases)	100	53	26	3(8)	29	6(4)	12	18	7	20	27	18	1	1	47	47
B.P. < 200/100	58	39	14	(2)	24	1(2)	4	8	6	7	15	5	1	—	19	32
B.P. > 200/100	42	14	12	3(6)	35	5(2)	8	31	1	13	33	13	—	1	28	66
Aortitis	25	19	3	—	12	1	1	8	1	2	12	2	—	—	5	20
Aortic heart disease (total cases)	30	13	14	(2)	47	(1)	1	3	3	11	47	1	—	—	15	50
with left ventricular hypertrophy and strain	15	7	8	—	53	—	—	—	—	8	53	—	—	—	8	53
with left ventricular hypertrophy	15	6	6	(2)	40	(1)	1	6	3	3	40	1	—	—	7	46
Mitral stenosis (total cases)	20	12	5	1	30	(1)	2(2)	10	—	—	—	—	8	—	8	40
with right ventricular hypertrophy and strain	10	5	5	—	50	—	(2)	—	—	—	—	—	5	—	5	50
with right ventricular hypertrophy	10	7	—	1	10	(1)	2	20	—	—	—	—	3	—	3	30
Congenital heart disease with right ventricular hypertrophy	20	7	13	(4)	65	(4)	(5)	—	—	—	—	—	13	—	13	65
Chronic cor pulmonale	20	18	—	—	—	—	2	10	—	—	—	2	—	—	2	10
Myocardial infarct (total cases)	80	40	37	(10)	46	3*	(2)	4	—	32	40	3	5	—	40	50
anterior	40	14	24	(6)	60	2	(2)	5	—	23	58	2	1	—	26	65
intramural	15	8	6	2	40	1	—	6	—	6	40	1	—	—	7	46
posterior	25	18	7	(2)	28	—	—	—	—	3	12	—	4‡	—	7	28
Coronary heart disease	50	35	5	(3)	10	4	4(6)	16	2	3	10	8	—	—	13	26
Hyperpotassemia	15	10	3	—	20	—	2	13	1	2	20	2	—	—	5	33
Hypoproteinemia	25	15	—	—	—	10†	—	40	—	—	—	10	—	—	10	40

Parentheses represent cases with other U, T-U abnormalities that have been already taken into account regarding the per cent proportion.

* Two cases with isoelectric U waves. † All 10 cases have isoelectric U waves. ‡ Posterior papillary muscle syndrome ?

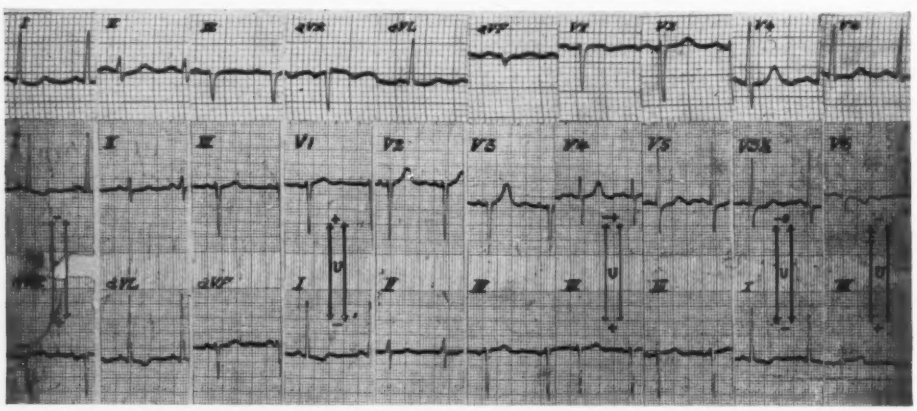

FIG. 3. Combined left papillary muscle syndrome. Negative U wave (leads I, V_L, V_4, V_5, V_6) combined with signs of left ventricular hypertrophy (upper tracing) and with left ventricular hypertrophy and strain 2 years later (lower tracing). Patient with hypertensive heart disease.

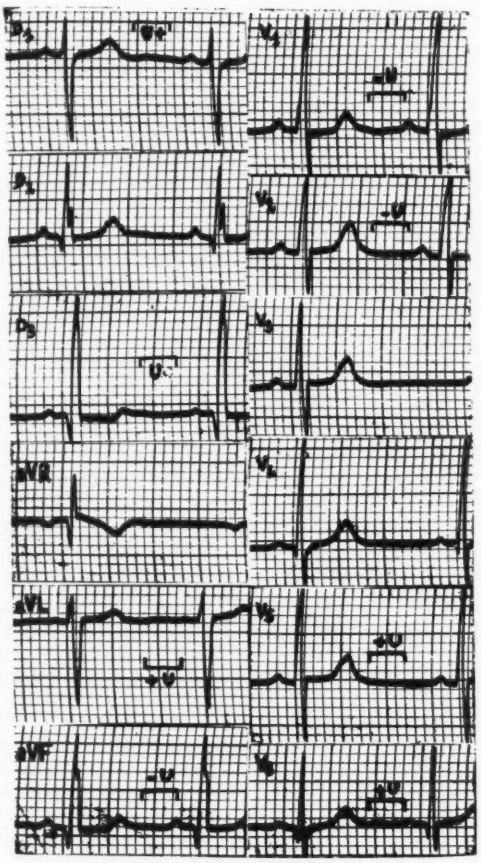

FIG. 4. Combined right papillary muscle syndrome. Negative U wave (leads III, V_1, V_2) combined with signs of right ventricular hypertrophy and strain. Patient with congenital heart disease (Fallot's tetralogy).

and in the right chest leads. The spatial U vector is directed anteriorly and to the left. Clinically, it is associated with right ventricular strain (mitral stenosis, congenital heart disease).

Biventricular Papillary Muscle Syndrome. Negative U waves appear in leads I, eventually in II, aV_L, and in all the chest leads. The spatial U vector is directed posteriorly and to the right. Clinically, there is strain of both ventricles (for instance, mitral stenosis with hypertensive heart disease).

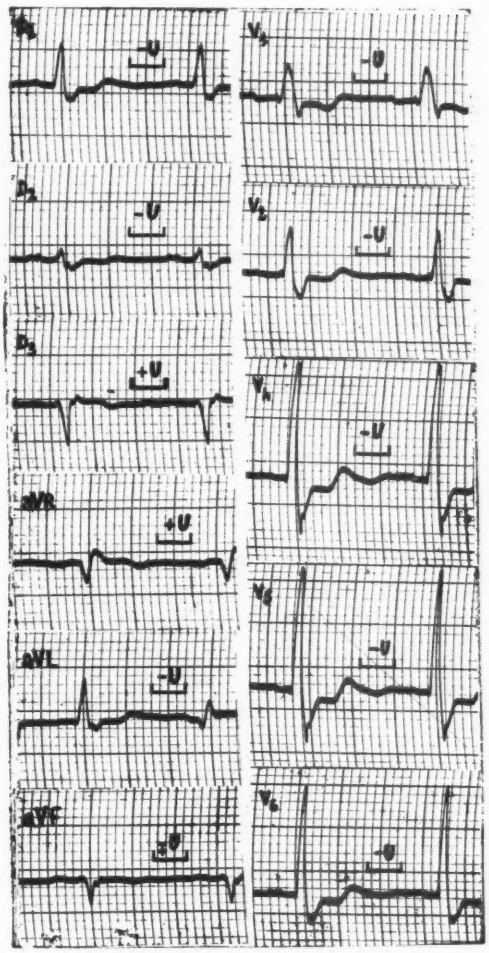

FIG. 5. Combined biventricular papillary muscle syndrome. Inverted U wave (leads I, V_L, and all chest leads) associated with the signs of right bundle-branch block and left ventricular hypertrophy. Patient with hypertensive heart disease, angina pectoris, and pulmonary fibrosis.

SEVERITY

The severity of the condition was also correlated with the type of U and T-U abnormality. We therefore differentiate a "minor" papillary muscle syndrome with minor alterations, such as very high or very low, positive U wave, transitory negative U wave, and pro-

longed T-U time, and a "major" papillary muscle syndrome with more significant changes, such as negativity or diphasism of the U wave and morphologic changes of the T-U segment.

Evolution

The alterations of the U wave and of the T-U segment may evolve in 2 ways in relation to the clinical course. They may regress with the regression or the disappearance of the precipitating causes. They may progress if the causes persist or develop further and lead to other electrocardiographic abnormalities.

Association with Other Electrocardiographic Abnormalities

We also differentiate between a "pure" papillary muscle syndrome, where the U and T-U changes are the only electrocardiographic abnormalities, and a "combined" papillary muscle syndrome, where the U and T-U changes are associated with other electrocardiographic alterations. As the pure syndrome is theoretically and practically the more significant, we shall emphasize it in our cases.

Incidence

Table 2 gives the incidence of the papillary muscle syndrome and its different types in the most common heart diseases.

In many cases of posterior myocardial infarction, the changes of the U wave are peculiar, in that they appear negative only in lead III and aV_F and not in the chest leads. It seems to us that such localization is not to be considered as an expression of strain of the right papillary muscles, but rather as a sign of a lesion of the posterior left papillary muscle, with a U spatial vector direct superiorly, anteriorly, and to the left. However, this hypothesis is not yet proved.

Table 3.—*Data Concerning Twenty-five Cases of Pure Left Papillary Muscle Syndrome*

No.	Sex	Age	Angle (°)			(—) U depth (.1 mm.)	Leads showing the (—) U	B.P.	Aorta enlarg.	Heart enlarg.	Dyspnea	Angina pectoris	Pulm. congestion
			$\widehat{QRS}$	$\widehat{T}$	$\widehat{U}$								
1	M	56	60	53	60	−3	V_5 V_6	120/75	++	++	+	+	+
2	M	60	32	28	60	−3	V_5 V_6	145/90	++	−	−	++	++
3	M	52	28	40	90	−3	V_4 V_5 V_6	205/110	+	++	++	−	−
4	M	53	68	55	−150	−3	I II III V_4 V_5 V_6	140/85	−	−	+	+	−
5	M	52	20	22	100	−1	I	190/110	+	−	+	+	+
6	M	59	28	70	?	−3	V_5 V_6	155/95	+	++	+	+	++
7	M	40	60	70	120	−3	I II V_5	138/85	−	−	−	++	−
8	F	46	53	30	100	−1	I V_L V_5	135/90	−	+	−	++	−
9	F	60	53	37	90	−3	V_4 V_5 V_6	135/85	−	−	++	++	++
10	M	56	10	48	120	−3	I V_4 V_5 V_6	215/140	+	+	++	−	++
11	M	50	60	28	10	−1	III V_6	180/135	−	+	++	++	++
12	F	38	45	18	0	−1	III V_6	180/100	−	++	++	−	++
13*	M	41	60	60	90	−3	V_5 V_6	160/90	−	−	++	−	++
14	F	58	14	10	100	−1	I V_L V_6	210/110	++	++	++	−	++
15	F	48	19	56	100	−1	I V_4 V_5 V_6	140/80	++	++	++	++	++
16	M	49	50	27	120	−3	I V_5	180/100	++	−	++	++	++
17	F	54	16	56	150	−3	I V_L	210/130	++	+	++	−	++
18	M	58	78	68	75	−3	V_L V_6	140/80	−	−	−	++	++
19	F	51	15	35	75	−3	V_L V_6	190/120	−	++	++	−	++
20	F	60	34	38	120	−3	I	220/112	++	++	++	−	++
21*	F	45	38	11	120	−3	I V_L	170/68	++	+	++	−	++
22	M	56	54	56	100	−3	I V_4 V_5 V_6	245/130	++	+	++	++	++
23*	M	26	66	57	?	−1	V_5 V_6	130/90	++	++	++	−	++
24	F	58	46	24	120	−3	I V_L	190/115	−	−	−	−	++
25	M	57	78	55	90	−3	V_5 V_6	240/130	++	−	++	−	++

* Aortic heart disease.

Clinical Cases

Combined Papillary Muscle Syndrome

Elsewhere we reported cases of the papillary muscle syndrome in which the alterations of the U wave and of the T-U segment are associated with other electrocardiographic abnormalities.[1] Figures 3–5 illustrate the 3 types of left, right, and biventricular papillary muscle syndrome.

Pure Papillary Muscle Syndrome

We use this term when the U and T-U changes are the only electrocardiographic abnormalities and the only evidence of underlying cardiac pathology. While we report extensively the clinical and physiologic data of the cases with electrocardiograms showing major abnormalities of the U wave and of the T-U segment, we are excluding as less significant the cases with minor pathology (high U wave, isoelectric U, prolonged T-U).

In our experience, there were no cases of pure right or biventricular papillary muscle syndrome. It seems, therefore, that in right ventricular and biventricular strain, isolated changes of the U wave and of the T-U segment do not appear, because the prevailing left ventricular potentials hide any sign of initial right ventricular pathology. On the contrary, the incidence of the pure left papillary muscle syndrome is appreciable, as 25 of 200 cases of negative U wave (out of 4,500 examined) were isolated.

The electrocardiographic characteristics of these 25 cases have been already described extensively,[9] and in table 3 we sum up their essential data. Figure 6 shows an electrocardiographic tracing in which the only abnormality is the inversion of U wave.

Age. The pure papillary muscle syndrome is characteristic of adults, not of the youngest or old age.

Sex. The incidence was greater in men. However, no substantial difference, from an electrocardiographic and clinical point of view, was found.

Enlargement of Heart and Aorta. As can be seen in table 3, we did not consistently find modification of the size of the heart and the aorta on fluoroscopy.

Pathogenesis. In our 25 cases of pure left papillary muscle syndrome, we have recognized strain of the left ventricle of extracardiac origin in 9 cases of hypertensive heart disease and in 3 cases of aortic heart disease; strain of the left ventricle of intracardiac origin in 9 cases of coronary insufficiency; and conditions of simultaneous extracardiac and intracardiac origin, in 4 cases of hypertensive heart disease with coronary insufficiency.

Therefore, we ought always to consider isolated alterations of the U wave and of the T-U segment as a sign of myocardial involvement. Consequently, the finding of a pure left papillary muscle syndrome allows us to make the diagnosis of heart disease.

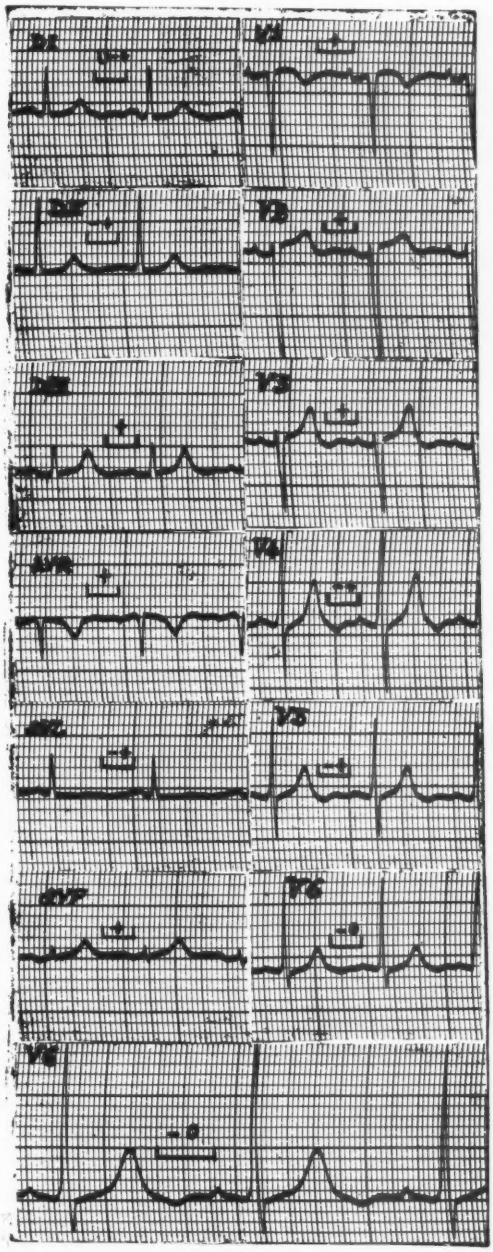

FIG. 6. Pure left papillary muscle syndrome. The negativity of the U wave (leads I, II, V_L, V_4, V_5, and V_6) is the only electrocardiographic abnormality. Patient with hypertensive heart disease.

Since isolated U and T-U alterations are an early and reversible abnormality,[1] appropriate treatment might cause return to normal of both the electrocardiogram and the clinical status.

Summary

Experimental and clinical documentation is presented of a new electrocardiographic and clinical entity: the syndrome of the papillary muscles. This documentation is schematized as follows:

1. We have demonstrated experimentally in dogs that the U wave originates from the papillary muscles of the ventricles.

2. The remarkable work of the papillary structures, during the ventricular systole and their presumed persistent contraction in the protodiastolic period, might explain the delay of their repolarization, as compared to that of the remaining myocardium. The U wave represents this retarded repolarization process.

3. We have specified all the possible alterations of the U wave and of the T-U segment. They are present only and always with pathologic cardiovascular conditions that involve the papillary muscles.

4. We have outlined different types of this papillary muscle syndrome, depending on variations in pathogenesis, site, severity, evolution, and presence of other electrocardiographic abnormalities. The incidence of the different types has also been determined in various cardiovascular diseases.

5. Finally, we have emphasized the clinical significance of the isolated alterations of the U wave and of the T-U segment (pure papillary muscle syndrome), since they are the only electrocardiographic manifestation of a diseased state, and they may regress with improvement of this condition.

Summario in Interlingua

Es presentate documentation experimental e clinic de un nove entitate electrocardiographic e clinic: le syndrome del musculos papillari. Iste documentation pote esser schematisate sequentemente:

1. Nos ha demonstrate experimentalmente in canes que le unda U ha su origine in le musculos papillari del ventriculos.

2. Le remarcabile labor del structuras papillari durante le systole ventricular e lor (supponite) contraction persistente durante le periodo protodiastolic explica possibilemente le retardo de lor repolarisation in comparation con le repolarisation del resto del myocardio. Le unda U representa iste retardate processo de repolarisation.

3. Nos ha determinate omne le possibile alterationes del unda U e del segmento T-U. Illos occurre solmente e semper con pathologic conditiones cardiovascular que affice le musculos papillari.

4. Nos ha delineate varie typos de iste syndrome del musculos papillari, secundo variationes de pathogenese, sito, severitate, evolution, e presentia o absentia de altere anormalitates electrocardiographic. Le incidentia del varie typos ha etiam essite determinate in varie morbos cardiovascular.

5. Finalmente, nos ha sublineate le signification clinic del isolate alterationes del unda U e del segmento T-U (pur syndrome de musculo papillari), proque illos es le sol manifestation electrocardiographic de un stato pathologic e pote regreder con le melioration del condition in question.

REFERENCES

1 Furbetta, D., Bufalari, A., and Santucci, F.: La parte terminale del ventricologramma—onda U e tratto TU—e la sindrome dei muscoli papillari. Rome, Società Editrice "Universo," 1955.

2 —, —, and —: Precisazioni e limiti delle caratteristiche elettrocardiografiche dell'onda U in condizioni normali. Folia cardiol. **14:** 339, 1955.

3 —, —, and —: Caratteristiche vettoriali dell'onda U in condizioni normali. Folia cardiol. **14:** 363, 1955.

4 —, —, and —: Rapporti cronologici tra l'onda U dell'elettrocardiogramma e i momenti del ciclo meccanico del cuore ad essa contemporanei. Folia cardiol. **14:** 457, 1955.

5 —, —, and —: Comportamento dell'onda U nei disturbi del ritmo cardiaco. Cuore e Circolazione **39:** 5, 1955.

6 —, —, and —: L'onda U nel quadro ecgrafico dell'infarto miocardico. Atti Accad. Med. Chir. Perugia **6:** 1, 1954–55.

[7] —, —, AND —: Comportamento dell'onda U dell' elettrocardiogramma nella ipertensione arteriosa. Cuore e Circolazione **40:** 3, 1956.

[8] —, SANTUCCI, F., AND BUFALARI, A.: Studio dell'onda U nelle prevalenze ventricolari e nei blocchi di branca. Atti Accad. Med. Chir. Perugia **6:** 30, 1954–55.

[9] —, —, AND —: Studio elettrocardiografico dell'onda U negativa. Atti Accad. Med. Chir. Perugia **6:** 54, 1954–55.

[10] —, —, AND —: Significato clinico dell'onda U negativa. Folia cardiol. **14:** 477, 1955.

[11] —, —, —, AND SOLINAS, P.: Morphological aspects of the negativity of U wave and their corresponding electrocardiographic and clinical data. Circulation **14:** 859, 1956.

HISTORICAL VIEW OF THE PROPERTIES OF DIGITALIS

Fuchsius in his hist. stirp. 1542, is the first author who notices it. From him it receives its name of Digitalis, in allusion to the German name of Fingerhut, which signifies a finger-stall, from the blossoms resembling the finger of a glove.

Sensible Qualities. Leaves bitterish, very nauseous. Lewis Mat. med. i. 342.

Sensible Effects. Some persons, soon after eating of a kind of omalade, into which the leaves of this, with those of several other plants, had entered as an ingredient, found themselves much indisposed, and were presently after attacked with vomitings. Dodonaeus pempt. 170.

It is a medicine which is proper only for strong constitutions, as it purges very violently, and excites excessive vomitings. Ray. hist. 767.

Boerhaave judges it to be of a poisonous nature, hist. plant. but Dr. Alston ranks it among those indigenous vegetables, "which, though now disregarded, are medicines of great virtue, and scarcely inferior to any that the Indies afford." Lewis Mat. med. i. p. 343.

Six or seven spoonfuls of the decoction produce nausea and vomiting, and purge; not without some marks of a deleterious quality. Haller hist. n. 330 from Aerial Infl. p. 49, 50.—WILLIAM WITHERING. *An Account of the Foxglove, and Some of Its Medical Uses.* Birmingham, 1785.

Nature of Rheumatic Fever

By MACLYN MCCARTY, M.D.

RHEUMATIC fever is now recognized as a systemic disease characterized by inflammatory lesions that may be widely distributed throughout the connective tissues in various parts of the body. Despite the generalized nature of the rheumatic process, it would be a disease of relatively little significance if it were not for involvement of the heart. This follows from the well-known fact that the lesions in most areas, such as the joints, appear to heal completely without detectable residual damage in contrast to those affecting the endocardium, which frequently lead to crippling malformations of the valves. Except for the currently uncommon cases in which overwhelming pancarditis or myocarditis threatens life during the acute phase of the disease, the menace of rheumatic fever can be defined almost solely in terms of this delayed and permanent effect on the valves of the heart. The seriousness of this end result of the disease justifies, and to a large extent stimulates, the continued attempts to clarify the mechanisms involved in the pathogenesis of acute rheumatic fever.

Not much insight is gained into the nature of rheumatic fever by classifying it as one of the "collagen diseases" or diseases of the connective tissue. The similarity of the basic mechanisms responsible for the various diseases included in this group has not been established; even if it is assumed that related processes are involved in each case, the fact remains that we are even more in the dark concerning the pathogenesis of the other diseases of connective tissue than we are in the case of rheumatic fever. Here, at least, we have clear evidence for a single inciting factor: infection with group A hemolytic streptococci. The relationship between the streptococcal infection and rheumatic fever is the point of attack of most current studies directed toward the problem of the fundamental nature of rheumatic fever, and, needless to say, there remain many gaps in our knowledge concerning this relationship. Even some of the broad aspects of the role of streptococci have not been settled; it is necessary, for example, to consider the problem of whether the presence of living streptococci is a primary requisite for rheumatic activity.

The concept that rheumatic fever can persist in the absence of viable streptococci arose from clinical observation and has been widely held by workers in this field. It was noted that during the interval between the acute streptococcal sore throat and the onset of rheumatic fever the organisms frequently disappeared from the upper respiratory tract or at least diminished in numbers to such an extent that they were no longer recoverable on culture. In fact, it was often necessary to establish the occurrence of a preceding streptococcal infection by employing serologic tests for antibodies. Although it was recognized that living streptococci might well be harbored within the tonsils or other areas inaccessible to the culture swab, other considerations led to the conclusion that persistent rheumatic activity did not depend on the presence of the organisms. Thus, the pathologic picture of the lesions of acute rheumatic fever did not appear comparable to those that result from direct bacterial infection. It was therefore assumed that something more subtle than the usual relationship between microorganism and infected tissue was concerned in the role of streptococci in rheumatic fever.

From the Rockefeller Institute for Medical Research, New York, N. Y.

This point of view received a challenge in 3 separate reports of postmortem bacteriologic findings published by Green,[1] Collis,[2] and by Thomson and Innes[3] in 1939 and 1940. Each of these papers was concerned with the recovery of hemolytic streptococci, some of which were identified serologically as the same type as that causing the original infection, from the heart valves of patients dying with rheumatic fever. Green reported positive cultures in 8 of 9 cases, Collis in 22 of 42 valves from 17 cases, and Thomson and Innes in 5 out of 10 cases. The technics employed were similar in each study, and postmortem blood cultures were quite generally negative in these cases. Collis was acutely aware of the pitfalls involved in attempting to base definite conclusions on this type of autopsy bacteriology, carried out under conditions in which the organisms may have been quite widely disseminated during the manipulations, and he recommended that similar studies be undertaken with special precautions to obtain material as soon as possible after death and with the use of aseptic technics patterned after those employed in surgery. In view of the importance of the information, it is regrettable that several different clinics did not find it possible to follow this recommendation, but concentration on the problem was apparently interrupted by World War II. The introduction of penicillin has now made repetition of these studies all but futile. The only known attempt to confirm these bacteriologic findings with more adequate technics prior to the availability of penicillin was carried out on a relatively limited scale and remains unpublished (Watson and Hirst, cited in reference 4), but the findings did not support the view that living streptococci are usually to be found in active endocardial lesions. In general, the participation of viable streptococci in the genesis of rheumatic lesions has been considered unproved, and most workers have continued to act on the working hypothesis that the streptococcal infection operates through some kind of indirect action.

The whole question of the role of living streptococci has now been reopened by the studies of the group at the Streptococcal Disease Laboratory of the Francis E. Warren Air Force Base. In pursuing their investigations on the prevention of rheumatic fever by treatment of streptococcal infections, these workers found that even when penicillin therapy was delayed for as long as 9 days after the onset of clinical pharyngitis, the incidence of rheumatic fever was sharply reduced in comparison with untreated or sulfadiazine-treated controls.[4] These results were interpreted quite logically as indicating that living streptococci may be required for the development and perpetuation of rheumatic fever. However, it seems to the present writer that the findings are susceptible to alternative interpretations. For example, it is conceivable that a quantitative "dosage factor" may be involved and that even delayed elimination of streptococci in certain cases will have the effect of holding the stimulus to a level below that which will result in the overt manifestation of rheumatic fever. There is relatively little information on the manner in which the body disposes of killed streptococci, and the amount of streptococcal products accumulated may depend to some extent on the duration of infection.

In any event, there are clinical observations that are difficult to reconcile with the concept that the living streptococcus is an essential component of the active rheumatic process. Most clinicians concerned with the follow-up care of a rheumatic population have observed instances of streptococcal disease in which even prompt and vigorous penicillin therapy did not prevent recurrence of rheumatic fever, and there is no good evidence that the severity or duration of the attack has been greatly affected. The chronic cases of rheumatic fever with unequivocal persistence of disease activity over a period of many months are also not easily explained on the basis of persistence of streptococci unless the organisms can remain latent in some fashion such as that described by Denny and Thomas in the case of rabbits infected intravenously with streptococci.[5]

One might suppose that the widespread use of penicillin therapy would have quickly settled the issue of the role of viable streptococci, and, indeed, the failure of this medication to affect the course of the disease has served to support the thesis that living organisms are not impor-

tant. However, it must be conceded that penicillin has not been employed in a way that would satisfy a critical proponent of the contrary thesis. It is now well established that the bactericidal effect of penicillin is exerted only on streptococci that are in the active phase of growth and that once growth and metabolism have stopped, the organisms may remain viable in the presence of concentrations of penicillin much above those that are lethal for growing cells. In view of this fact, a test of the effect of penicillin on the course of rheumatic fever would require more massive doses and more prolonged administration than are ordinarily used, and in addition should probably include the concomitant use of cortisone in an attempt to reactivate metabolically inert streptococci. Further studies are obviously needed to solve this basic problem.

Clarification of the role of living streptococci is important not only because of the implications with regard to the clinical management of rheumatic fever. This information is also needed in determining the direction to be taken by future studies on the mechanism by which streptococci induce the disease. It has been pointed out that the protective effect of delayed penicillin therapy in the study discussed above throws doubt on hypotheses that explain the pathogenesis of rheumatic fever either on the basis of a direct toxic action of some streptococcal substance or on the formation of autoantibodies.[4] On the other hand, the results tend to support the thesis that a hypersensitivity reaction to some streptococcal antigen is involved. This, in turn, is in harmony with the most widely held view regarding the pathogenesis of the disease, since the majority of workers in the field are operating on the assumption that hypersensitivity, or at least some form of antigen-antibody interaction, is involved in the basic pathologic process.

Despite the general adherence to this point of view and its attractiveness as an hypothesis, proof of the role of hypersensitivity depends upon fragments of indirect evidence that cannot be considered conclusive. There is no information concerning the nature of the antigen-antibody system involved except for the strong implication that the antigen is probably of streptococcal origin. The type of evidence on which the hypersensitivity theory is based include the following: (1) the similarity of the latent interval that separates the streptococcal infection and the onset of rheumatic fever to the time required to attain maximal antibody response after an antigenic stimulus; (2) the resemblance of certain manifestations of rheumatic fever to those of serum sickness; (3) the suggestive similarity of the lesions of rheumatic fever to those obtained in studies of experimental hypersensitivity in animals; and (4) the fact that rheumatic subjects on the average show a greater antibody response to various streptococcal antigens than do patients with uncomplicated streptococcal infections in the same epidemic.

The finding that patients with rheumatic fever have a greater mean antibody response to streptococcal antigens has been amply established by several independent studies. Similar results have been obtained with each of several antibodies, but there is always overlapping between the antibody titers of the rheumatic and nonrheumatic groups so that the differences are not absolute and have little diagnostic value. Nevertheless, this indication of an altered immune response must be considered of possible significance in the pathogenesis of rheumatic fever, and it has led to the concept that exaggerated immunologic reactivity may be an essential component of the rheumatic diathesis. A number of different investigators have attempted to test this concept by comparing the response of normal and rheumatic individuals to the injection of various nonstreptococcal antigens. Unfortunately, the results obtained have not been in complete agreement. Creger, Choy, and Rantz[6] found some evidence for hyperreactivity on the part of rheumatic subjects injected with such antigens as heterologous human erythrocytes, but the numbers of patients involved were too small to allow definite conclusions. Miller, Kibrick, and Massell[7] observed a small increase in the mean titer of typhoid agglutinins in rheumatic patients as compared with controls after the injection of typhoid vaccine. The most definitely positive results in studies of this type were reported by Wagner and Rejholec[8] who em-

ployed a *Brucella abortus* vaccine. They found a statistically significant difference in the titer of agglutinins, but an even more definite difference in the occurrence of incomplete antibodies as measured by the Coombs technic.

In contrast to these studies, completely negative results were obtained by other workers using a variety of antigens, including pneumococcal polysaccharide,[9] influenza virus vaccine,[7] and diphtheria toxoid.[10, 11] No differences between rheumatic subjects and controls were found with still other antigens in extensive unpublished work carried out at Fort Warren (cited in reference 12). The experiments in which diphtheria toxoid was employed as antigen are of special interest for 2 reasons. In the first place, nonprecipitating antibodies were measured in addition to precipitins and the capacity of the sera to neutralize toxin in vivo. Since no difference was detectable in the formation of nonprecipitating antibodies by rheumatic and nonrheumatic subjects, it is evident that the results obtained by Wagner and Rejholec with incomplete antibodies to brucella do not represent a general phenomenon for this type of antibody. The second point of interest in the diphtheria toxoid studies is that only Schick-negative subjects were used, and consequently the booster type of antibody response was elicited. In theory, this should be more comparable to the situation in rheumatic fever, since the patient has almost certainly had one or more previous experiences with streptococcal antigens and the antigenic stimulus of a streptococcal infection preceding rheumatic fever would simulate that of a booster injection.

In summary, most of these efforts to obtain experimental evidence of hyperreactivity have revealed little or no difference between rheumatic patients and controls in the response to a variety of antigens. Certainly nothing comparable to the naturally occurring increased response to streptococcal antigens has been observed, and it is necessary to conclude that the theory of general immunologic hyperreactivity of rheumatic subjects has not been supported. There are, of course, other possible explanations for the enhanced streptococcal antibody response in rheumatic fever. For example, it may be a reflection of a conditioning process resulting from greater previous experience of the susceptible individual with streptococcal infection. Alternatively, it may reflect a quantitatively greater antigenic stimulus that is not necessarily manifested by greater clinical severity of the streptococcal infection that precedes the attack of rheumatic fever. Regardless of the explanation for the pattern of immune response in rheumatic fever, the demonstration of hyperreactivity contributes to the continued emphasis on the probable role of antigen-antibody mechanisms in the disease.

Much of the work on the relationship of streptococci to rheumatic fever has as its goal the identification of the specific streptococcal component or components that are of primary importance, either as antigens or as biologically active substances with some direct action on the tissues. The difficulty with this approach has been the lack of criteria that would allow one to determine whether a given substance is implicated or should be eliminated as of no consequence. Up to the present time no experimental model has been devised that makes it possible to carry out an unequivocal test of the rheumatogenic potentiality of various substances in a laboratory animal. Individual investigators have interpreted and weighted the available evidence in many ways with the result that widely varying emphasis governs the attack employed in different laboratories. This diversification of approach is highly desirable in that the uncertainties concerning the mode of action of the streptococcus demand that a variety of points of view be brought to bear on the problem.

The investigator must look for clues to the mechanism of the disease in the clinical pattern and natural history of rheumatic fever. Thus, the subacute and chronic cases, in which the whole range of clinical manifestations of the disease may persist despite the progressive elapse of time from the inciting streptococcal infection, must be taken into consideration in the formation of hypotheses regarding the role of streptococci. Admittedly, if living streptococci are indeed associated with perpetuation of the disease, this pattern of the rheumatic

process affords little assistance in narrowing down the possible modes of action of streptococci, since all of the various components and potentialities of the organism would be present. On the other hand, if the disease can continue in the absence of living cells, the investigator's attention must turn to a search for ways in which the initiating infection can have such a protracted effect. If one chooses to base a theory on the framework of a streptococcal antigen-antibody reaction, it is possible to invoke the evidence obtained by experimental immunologists that even in the case of soluble antigens at least a small portion may remain in the tissue for long periods of time. Thus, it is conceivable that certain antigens released by streptococcal cells either during growth, as in the case of the several extracellular antigens, or upon disintegration of the organism may remain localized in some tissues long after the infection has been eliminated. The possibility of an additional potential source of retained bacterial products is suggested by the properties of the streptococcal cell wall. This rigid structural portion of the cell, which contains the group-specific polysaccharide as an integral component, is highly resistant to dissolution under physiologic conditions. Although microbial enzymes have been found that will lyse the cell wall, it has not been possible to demonstrate comparable enzymes in human tissues. Unless some unknown mechanism exists for dealing with this material, elimination of residual cell walls following phagocytosis and partial digestion of streptococci may be an inefficient and prolonged process.

The chronic cases of clinically manifest rheumatic fever obviously pose special problems in the understanding of the nature of the disease, but perhaps an even more perplexing question arises from the implications of the finding of Aschoff bodies in the auricular appendages of a large number of patients undergoing commissurotomy for mitral stenosis. For the most part, these patients show no clinical or laboratory evidence of rheumatic activity, and if one accepts the occurrence of Aschoff nodules as unequivocal evidence of disease activity it is necessary to assume that the process continues at a subclinical level almost indefinitely in a substantial proportion of cases. This assumption would be of considerable significance in the study of the mechanisms concerned in rheumatic fever, and it is important both for the clinician to re-examine his criteria for rheumatic activity and for the pathologist to evaluate carefully the group of lesions classed together as Aschoff bodies. One pathologist has expressed the opinion that the lesions found in the auricular appendages obtained at operation do not have the typical structure of Aschoff bodies and are not characteristically distributed throughout all 3 layers of the heart.[13] He concluded that the prevalence of these lesions did not justify a redefinition of the active rheumatic process.

In one of the most recent reports on this subject[14] the authors attempted to divide the lesions found on biopsy of the auricular appendage into 2 types: the atypical lesions that were static in appearance and those showing findings consistent with an early or fresh lesion. As criteria for the latter type they selected the following: fragmentation of collagen fibers, alterations in the ground substance, degeneration of myofibers, and the occurrence of exudative inflammatory reaction in or around the lesion. On the basis of these criteria they found evidence of active lesions in only 2 per cent of the cases studied (8 of 400). This figure is not quite so overwhelming as that obtained in conventional studies in which one-third or more of the biopsies are interpreted as showing evidence of Aschoff bodies, and it seems more reasonable to fit these findings into the accepted pattern of the origin of rheumatic activity. These 8 patients showed no clinical evidence of activity, although the generally negative laboratory studies included definitely elevated sedimentation rates in 5 of the 8 cases. Antistreptolysin O titers are stated to have been noncontributory, but it is evident that a more intensive search for indication of a recent experience with streptococci is indicated in cases of this type. While it is too early to draw final conclusions on the implications of the biopsy data, the current status of the problem strongly suggests that it is unnecessary to assume that the rheumatic process can persist indefinitely without the repeated stimulus of streptococcal infection. On the other hand, it will not be surprising if it is demonstrated that some degree of rheumatic activity can occur in the absence of clinical and

laboratory findings, since there is almost certainly a threshold level below which the magnitude of an inflammatory process is too small to cause symptoms or detectable changes in the currently available tests for inflammation.

The preceding discussion emphasizes the defects that exist in our understanding of the chain of events leading from an infection with hemolytic streptococci to the occurrence of rheumatic fever. There is an evident need for continued investigation of various phases of the problem, ranging from studies on the behavior of the organism in host tissues and of the host reaction to its presence to further basic studies on the biology of the streptococcus. The role of the streptococcus has been stressed—some may think overstressed—to the virtual exclusion of other considerations that may bear on the pathogenesis of the disease. However, it is obvious that other factors play a role in the disease, not only because relatively few individuals appear to be susceptible and only a small percentage of streptococcal infections lead to rheumatic fever, but also because practically all diseases are modified to some degree by environmental and host factors. Nevertheless, the inciting action of streptococcal infections in rheumatic fever is the one key available that promises to provide information on the fundamental nature of the disease, and as mentioned above, it is this relationship to a specific bacterial agent that sets rheumatic fever apart from the other diseases of connective tissue. In any event, the problem of the role of the streptococcus must certainly be solved and the solution may at the same time lead to an understanding of the other factors that modify the pathogenetic effect of the organism.

REFERENCES

[1] Green, C. A.: Researches into the aetiology of acute rheumatism. I. Rheumatic carditis: Post-mortem investigation of nine consecutive cases. Ann. Rheumat. Dis. **1:** 86, 1939.

[2] Collis, W. R. F.: Bacteriology of rheumatic fever. Lancet **2:** 817, 1939.

[3] Thomson, S., and Innes, J.: Haemolytic streptococci in cardiac lesions of acute rheumatism. Brit. M. J. **2:** 736, 1940.

[4] Catanzaro, F. J., Stetson, C. A., Morris, A. J., Chamovitz, R., Rammelkamp, C. H., Jr., Stolzer, B. L., and Perry, W. D.: The role of the streptococcus in the pathogenesis of rheumatic fever. Am. J. Med. **17:** 749, 1954.

[5] Denny, F. W., Jr., and Thomas, L.: Persistence of group A streptococci in tissues of rabbits after infection. Proc. Soc. Exper. Biol. & Med. **88:** 260, 1955.

[6] Creger, W. P., Choy, S. H., and Rantz, L. A.: Experimental determination of the hypersensitive diathesis in man. J. Immunol. **66:** 445, 1951.

[7] Miller, J. M., Kibrick, S., and Massell, B. F.: Antibody response to non-streptococcal antigens as related to rheumatic fever susceptibility. J. Clin. Invest. **32:** 691, 1953.

[8] Wagner, V., and Rejholec, V.: Agglutinins and incomplete antibodies after a single antigenic inoculation in normal and rheumatic individuals. Ann. Rheum. Dis. **14:** 243, 1955.

[9] Quinn, R. W., Seastone, C. V., and Dickie, H. A.: Antibody production and tuberculin sensitivity in individuals with a history of rheumatic fever. J. Immunol. **70:** 493, 1953.

[10] Kuhns, W. J., and McCarty, M.: Studies of diphtheria antitoxin in rheumatic fever subjects: Analysis of reactions to the Schick test and of antitoxin responses following hyperimmunization with diphtheria toxoid. J. Clin. Invest. **33:** 759, 1954.

[11] Quinn, R. W.: The antitoxin response of Schick-negative rheumatic and non-rheumatic subjects to diphtheria toxoid. J. Immunol. **76:** 246, 1956.

[12] Stetson, C. A.: The relation of antibody response to rheumatic fever. *In*, Streptococcal infections, M. McCarty, Ed., New York, Columbia Univ Press, 1954, p. 208.

[13] Enticknap, J. B.: Biospy of the left auricle in mitral stenosis. Brit. Heart J. **15:** 37, 1953.

[14] Tedeschi, C. G., and Wagner, B. M.: The problem of subclinical rheumatic carditis. Am. J. M. Sc. **231:** 382, 1956.

Prophylaxis of Rheumatic Fever

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GROUP A streptococcal infection initiates acute rheumatic fever; rheumatic valvular heart disease is a sequela that develops during or subsequent to the acute rheumatic episode. The mechanism by which the preceding streptococcal infection produces the arthritic and constitutional symptoms and valvular heart disease is unknown. Regardless of the mechanism involved, there is little doubt that prevention of the streptococcal infection eliminates acute rheumatic fever and presumably rheumatic heart disease in any population group. This fact has guided the management of a selected group of individuals, namely those patients who have already had 1 attack of rheumatic fever. The continuous prophylactic administration of a sulfonamide drug or penicillin is a widely practiced measure for ensuring freedom from streptococcal infections and rheumatic recurrences.

The establishment of the relationship of the streptococcal infection to acute rheumatic fever led to the development of other methods for the control of rheumatic fever, since it was logical to believe that successful treatment of the original streptococcal respiratory disease might alter the attack rate of this nonsuppurative complication. Treatment with sulfonamides failed to prevent rheumatic fever[1, 2] in spite of the favorable influence it exerted on the natural course of the acute respiratory illness. Subsequently, penicillin was employed by Massell, Dow, and Jones[3] for the therapy of streptococcal infections in patients who had experienced 1 or more rheumatic episodes and recurrent attacks of rheumatic fever were eliminated. Similarly, initial attacks of rheumatic fever may be prevented by successful treatment of the streptococcal illness with penicillin or other antibiotics.[4]

On the basis of this and other information, the American Heart Association[5] has made recommendations for the control of rheumatic fever that are summarized in table 1. Minor changes in the methods employed in prophylaxis and treatment of streptococcal infections undoubtedly will be made as experience accumulates. For example, the duration of protection afforded by various doses of benzathine penicillin has not been determined nor has the daily oral dose of penicillin prophylaxis been finally established. Recent evidence[6] indicates that 1,200,000 units of benzathine penicillin will protect against streptococcal infections for 6 weeks and 900,000 units for 4 weeks. Likewise, oral penicillin probably should be administered in doses of 200,000 units twice daily to insure adequate prophylaxis.

It appears unlikely that major revisions in these recommendations will be made unless new data become available that invalidate previous conclusions. Recently, serious doubts have been raised as to whether successful treatment of streptococcal infections does indeed prevent valvular heart disease. In addition, some physicians have questioned the desirability of continuing prophylaxis for life in those individuals who have experienced 1 or more rheumatic attacks. It is the purpose of the present discussion to review some of the data and considerations presently available regarding these 2 aspects of the problem of rheumatic fever.

Does Treatment of the Streptococcal Infection Prevent Rheumatic Heart Disease as Well as Symptoms of Acute Rheumatic Fever?

It is apparent from various studies that treatment of the streptococcal illness results in a decreased incidence of the clinical manifesta-

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TABLE 1.—*Recommended Procedures for the Prevention of Rheumatic Fever**

Treatment of Streptococcal Infections by One of the Following Methods	
Benzathine penicillin G intramuscularly	
Children:	One injection of 600,000 units
Adults:	One injection of 600,000 to 900,000 units
Procaine penicillin with 2 per cent aluminum monostearate in oil intramuscularly	
Children:	One injection of 300,000 units every 3 days for 3 doses
Adults:	One injection of 600,000 units every 3 days for 3 doses
Oral penicillin	
Children:	250,000 units 3 times a day for 10 days
Adults:	250,000 units 3 times a day for 10 days
Broad spectrum antibiotics	
Therapeutic doses for at least 10 days	
Prevention of Streptococcal Infections in Rheumatic Individuals	
Continuous prophylaxis for life by 1 of the following methods:	
Intramuscular benzathine penicillin G	1,200,000 once a month
Sulfadiazine:	0.5 to 1.0 Gm. once daily
Oral penicillin:	200,000 to 250,000 units daily

* As recommended by the American Heart Association. The order of medication is the order preferred by the authors.[5]

tions of acute rheumatic fever. In the first demonstration of this fact, Massell, Dow, and Jones[3] showed that the administration of penicillin prevented recurrences in 15 patients with streptococcal infections who had experienced rheumatic fever previously. These studies were extended to include a group of patients observed during 36 streptococcal infections.[7] Patients with 11 of these infections received no therapy and served as controls and rheumatic recurrences occurred in 6 instances. In contrast, only 2 recurrences developed following the 25 infections treated with penicillin. The 2 recurrences in this treated group occurred in the 2 individuals who continued to harbor streptococci in the oropharynx.

In 1953 Breese[8] reported 1,204 streptococcal infections in 792 infants and children, all treated with penicillin or other antibiotics. Subsequent attacks of rheumatic fever were observed in only 1 instance. In spite of the lack of controls, this appears to be a remarkably low incidence of rheumatic sequelae.

The most extensive controlled studies have been conducted among men in military populations. In 1951 Wannamaker and associates[9] employed penicillin in 1 of 3 dosage schedules in the treatment of 1,178 patients with exudative tonsillitis and pharyngitis, and 1,162 patients served as controls, receiving no specific therapy. Within 45 days after the onset of the streptococcal infection, 2 patients who had received penicillin developed acute rheumatic fever, whereas this complication occurred in 28 of the control group.

Treatment with 1 of 2 broad spectrum antibiotics also reduced the attack rate of acute rheumatic fever, but the results were not so striking as those obtained following the use of penicillin. In a series of 1,009 patients who received chlortetracycline, 5 developed rheumatic fever, whereas 20 of 1,035 controls incurred this complication.[10] In a comparable study[11] in which oxytetracycline was employed as therapy of streptococcal exudative pharyngitis, rheumatic fever occurred within 35 days in 12 of 480 untreated controls and in 5 of 506 patients who received treatment.

The results of these studies indicate beyond doubt that successful treatment of the preceding streptococcal infection decreases the frequency of acute clinical attacks of rheumatic fever. Analysis of the failures to prevent acute rheumatic fever by the treatment of the preceding streptococcal infection with 1 of the antibiotic drugs showed that any form of treatment that does not eliminate the infecting organism was not satisfactory.[6] Thus, in those individuals with streptococcal infections whose organism was not eliminated by therapy, the attack rate of rheumatic fever was not appreciably different from that observed in patients receiving no therapy. The importance of the living streptococcus in the production of acute rheumatic fever is also emphasized by the fact that sulfadiazine, a bacteriostatic agent, does not eliminate the organism when administered to patients with streptococcal pharyngitis and does not decrease the attack rate of acute rheumatic fever.[2] Therefore, in the evaluation of

various therapeutic regimens for prevention of rheumatic fever by treatment of the preceding streptococcal infection, it becomes necessary to examine the bacteriologic results.

Primarily on the basis of the above studies the American Heart Association made recommendations for the prevention of rheumatic fever. Until evidence to the contrary is produced, it was logical to assume that prevention of the acute joint and constitutional symptoms of rheumatic fever would result in a decreased incidence of rheumatic valvular heart disease. Recently, Weinstein, Boyer, and Goldfield[12] have produced some data that indicate that treatment of the preceding respiratory illness prevents the symptoms of acute rheumatic fever but not valvular heart disease. In their initial studies[13] electrocardiographic abnormalities developed in patients with scarlet fever during early and late convalescence and this was considered as evidence that rheumatic carditis was not prevented by therapy. Subsequent follow-up studies[12] confirmed this impression, since rheumatic valvular heart disease appeared in most of those patients who exhibited abnormalities and did not appear in those with normal electrocardiograms.

In Weinstein's study[12] 167 patients with scarlet fever were treated with penicillin. Forty of these received 800,000 units orally each day for 10 days; 127 were given 120,000 units intramuscularly daily for 10 days. During convalescence 12 patients (7.2 per cent) developed symptoms and signs suggestive of rheumatic fever and of these, 2 met the diagnostic criteria employed by Jones.[14] The other 10 patients demonstrated electrocardiographic changes and in a few of these vague symptoms were also recorded. Seven years later 110 of the original 167 patients returned for study, including 10 of the original 12 suspected of having acute rheumatic fever.[13] None of the 100 patients available for examination who had had no findings suggestive of rheumatic fever earlier showed findings indicative of valvular heart disease. Of the 10 patients diagnosed as possible rheumatic fever only 2 were thought to have normal hearts at this follow-up examination and 8 exhibited signs indicative of rheumatic valvular heart disease.

The fact that valvular heart disease developed in those patients exhibiting electrocardiographic changes during the acute streptococcal infection and early convalescence led the authors to suggest that treatment of the original streptococcal infection prevented the acute clinical manifestations of rheumatic fever but not valvular deformities. This situation might be considered analogous to the effects of ACTH and cortisone, which suppress the clinical manifestations but not valvular heart disease when administered during an attack of acute rheumatic fever.[15] If these observations of Weinstein[12] are confirmed, the failure to prevent valvular deformities by treatment of the streptococcal infection with penicillin suggests that the mechanisms of production of joint disease and heart disease are different. Furthermore, if treatment of the streptococcal infection does not reduce the incidence of valvular heart disease, other methods of accomplishing this goal should be pursued vigorously. Although final answers are not yet available, certain data would indicate that adequate treatment of the acute respiratory infection may alter the incidence of rheumatic carditis.

There are a number of studies of electrocardiographic changes subsequent to scarlet fever and streptococcal pharyngitis. Faulkner, Place, and Ohler[16] observed changes in the T wave in leads I or II or prolongation of the P-R interval to 0.20 sec. or longer in 6 per cent of 171 patients with scarlet fever who received no specific treatment. Roelsen[17] found a prolonged P-R interval of 0.20 sec. or more in 16 per cent of 108 patients with scarlet fever and arthralgia and in 4 per cent of 99 scarlet fever patients without arthralgia. In these 2 studies no specific antibacterial treatment was employed. Watson, Rothbard, and Swift[18] studied 110 adults with scarlet fever who received either sulfadiazine or no specific therapy. Twenty-two or 20 per cent showed electrocardiographic abnormalities at some time during the illness. Fifteen of the 22 patients exhibited an increase of the P-R interval of 0.04 sec. or more. Seven showed inverted T waves in leads I or II. In this total group of 22 patients there were 6 definite and 2 probable

cases of active rheumatic fever. Rantz, Spink, and Boisvert[19] performed serial electrocardiograms on 185 of 410 soldiers with streptococcal pharyngitis of whom 14.9 per cent received small amounts of penicillin and the remainder sulfonamides or only symptomatic therapy. Of the 185 patients studied 31 (16.7 per cent) showed definite prolongation of the P-R interval or flat or inverted T waves in leads I and II. Nine of these 31 patients were thought to have rheumatic fever.

In 1952, Levander-Lindgren[20] described the results of electrocardiographic studies on 2,831 children and adults with scarlet fever. Most of the patients were treated with penicillin and about 20 per cent served as controls. T-wave abnormalities or P-R interval changes occurred in 3.3 per cent. This low incidence of abnormalities may have been influenced by the infrequency with which tracings were obtained compared to other series. Ninety-six of the 110 patients with all types of electrocardiographic changes were examined 1 to 5 years later and of these only 1 patient showed auscultatory evidence of valvular heart disease. This observation does not confirm the results reported by Weinstein.[12]

These several studies demonstrate that electrocardiographic changes of the type described by Weinstein, Bachrach, and Boyer[13] occur fairly frequently during convalescence from streptococcal infections. They have been noted in other acute infections and all of them are not necessarily indicative of rheumatic carditis.[21]

The question whether penicillin treatment of streptococcal infections alters the frequency of these changes may be answered by 2 studies. Levander-Lindgren[20] stated that penicillin seemed to decrease the frequency of severe electrocardiographic changes in adults but otherwise had little or no effect. However, review of her data, excluding from consideration a group of patients whose therapy was withheld for 5 days, shows that changes occurred in 4.9 per cent of controls as compared to 3.2 per cent in the cases receiving penicillin. A more striking difference was observed by Hahn[22] in studies in a military population. Abnormalities, including prolongation of the P-R interval to 0.21 sec. or by an increment of at least 0.04 sec., inversion of the T wave in leads I or II, and prolongation of the Q-T interval occurred in 11.2 per cent of 566 untreated controls subsequent to streptococcal pharyngitis. Treatment with penicillin or broad-spectrum antibiotics in 724 patients was associated with an incidence of these abnormalities of only 5.2 per cent, a highly significant difference. If the electrocardiographic changes are specific and indicate rheumatic carditis, the data obtained by Hahn[22] would suggest that the incidence of specific carditis was decreased by treatment. It is also possible that treatment prevented only nonspecific changes rather than the abnormalities associated with rheumatic carditis.

A remarkable finding in the report of Weinstein[12] is the very high incidence of valvular heart disease found 7 years later in the 10 patients with electrocardiographic abnormalities. That 8 of these 10 showed evidence of rheumatic heart disease at follow-up examination in contrast to none of those whose tracings 7 years earlier were normal suggests that these electrocardiographic changes presage the development of valvular heart disease with remarkable accuracy and that their absence is a reassuring prognostic sign. It is difficult to reconcile these results with studies on patients with symptoms of acute rheumatic fever. For example, Stolzer, Houser, and Clark[23] studied 138 patients who had daily electrocardiograms for the first 3 weeks and every other day for the next 6 weeks. All patients were maintained on prophylaxis and examined 14 months later for evidence of valvular heart disease. Approximately 50 per cent of the group showed abnormal prolongation of A-V conduction during the course of acute rheumatic fever, and of this group only 38 per cent were found to exhibit valvular heart disease 14 months later. In contrast, 22 per cent of those patients who showed no abnormal atrioventricular conduction exhibited valvular heart disease at the time of the final examination. Thus, in this study abnormal prolongation of the P-R interval did not necessarily foretell the development of valvular heart disease and valvular abnormalities developed frequently in the absence of prolongation of the conduction time.

As mentioned above, in order to decrease the attack rate of rheumatic fever by treatment of the preceding respiratory infection, it is probably necessary to eradicate the group A streptococcus. In the series of Weinstein[12] 33 per cent of all patients with scarlet fever are known to have developed a bacteriologic relapse or reinfection after cessation of therapy with penicillin. It is not clear from their reports how many of the 12 patients suspected of having rheumatic fever incurred such relapses. However, upon re-examination of the data[24] cultures from 8 patients showed no group A streptococci at the time rheumatic fever was first suspected or during the rheumatic episode. In 1 instance streptococci reappeared in the pharynx prior to the development of rheumatic symptoms, and from 3 individuals streptococci were isolated following the first sign of rheumatic fever. Thus, in this small group of patients streptococci were isolated from the pharynx no more frequently in the suspected rheumatic group than in the entire series.

Final answers to the disturbing questions raised by the study of Weinstein[12] are unavailable at present. There is no doubt that treatment of the preceding streptococcal infection decreases the incidence of rheumatic fever providing the treatment is adequate to eliminate the organism. It has also been shown by Hahn[22] that such treatment prevents, in large part, the electrocardiographic changes frequently observed following streptococcal infections. However, the answer to the question whether treatment of the streptococcal infection prevents rheumatic valvular deformities must await information that can be obtained only from a controlled study. Until such information is available, it would seem advisable to continue to treat acute streptococcal diseases with therapy known to eliminate the organism in the majority of instances.

How Long Should Prophylaxis Be Maintained in the Patient Who has had Rheumatic Fever?

In order to plan a rational method of management of the patient who has experienced rheumatic fever the physician should be acquainted with certain epidemiologic features of streptococcal infections and rheumatic fever. Group A streptococci are maintained in nature in the upper respiratory tract of man. The most dangerous source of infections is the carrier who has recently acquired the organism.[25] Since streptococcal infections occur frequently in the young, school-age child, any situation that places the individual in contact with children increases the risk of infection. The organism is transferred to the susceptible host by *intimate contact* and not by droplet nuclei, contaminated dust, bedding, and other articles.[25]

Although adults apparently acquire fewer streptococcal infections than children, it is probably a fallacy to believe that this is due to acquired resistance. Immunity in man is type-specific and relatively long enduring.[25, 26] Since most adults probably have had experience with only a few serologic types during childhood, they should become infected if adequately exposed to a carrier harboring a new type of streptococcus. Experience in military populations shows that young adults are very susceptible to these infections when assigned to an installation experiencing an epidemic.

Although type-specific immunity to streptococcal infections may play a minor role in the decreased incidence of both initial and recurrent attacks of rheumatic fever in older age groups, the major factor is most likely the lack of effective contacts with carriers of the organism. Another factor that may contribute to the low rates of initial attacks of rheumatic fever in the adult is decreased susceptibility to rheumatic fever following a streptococcal infection.[12] Although the data are meager, available information indicates that the rates are not influenced by age,* once a streptococcal infection develops.[27] The situation in relation to the risk of recurrence of rheumatic activity as age progresses is poorly defined, but it is generally agreed that 1 attack confers a marked increase in susceptibility.

The reported rates of recurrence from 3 studies are shown in table 2. Although the figures vary among the 3 studies, it is apparent

* Attack rates of rheumatic fever following the first experience with the organism are not available.

TABLE 2.—*Per cent of Patients Developing Recurrences at Five-Year Intervals after the Original Attack*

Author	Year	Years after initial attack			
		1–5 (%)	6–10 (%)	11–15 (%)	16–20 (%)
Kaiser[28]	1934	89	25	—	—
Ash[29]	1948	63	5	—	—
Bland and Jones[30]	1951	76	57	30	7

that the number of recurrences diminished with succeeding years. Nonetheless, the data of Bland and Jones[30] show a relatively high rate of recurrence 10 to 20 years after the original bout of rheumatic fever, indicating that a considerable risk still obtains in early adult life. Leonard[31] found that annual recurrence rates depended on age at onset and varied between 10 and 23 per cent 5 years after the initial attack and between 5 and 10 per cent 9 years after the first attack.

In an extensive study comprising 3,129 patients with approximately 6,000 recurrences, Cohn and Lingg[32] in 1943 published information regarding yearly recurrence rates. The recurrence rates may be somewhat high in this study, since patients with ill-defined "subacute activity" were included. Recurrent attacks fell gradually from rates ranging between 10 and 40 per cent initially, depending on age, to rates of between 5 and 19 per cent per year by early adult life and then persisted at this level. The group whose initial attack occurred prior to 5 years of age was an exception to this; 15 years later recurrences still occurred yearly in 15 to 25 per cent of this group. The results of these studies indicate that risks of recurrences are high as late as 15 to 20 years after the original attack, but they do not define the effect of freedom from activity on the susceptibility to recurrence. Here again, the available data are few.

Wilson and Lubschez,[33] employing a life table technic, studied 499 rheumatic patients who experienced a total of 817 recurrences. Thirty-one per cent of the original group did not experience a recurrence. The risk for a major recurrence (arthritis, chorea, or active carditis, alone or in combination) was 20.6 per cent in the first year following an attack, 10.7 per cent following 1 year of freedom from activity, and 6.6 per cent following 2 or more years of freedom. The recurrence rate in children was higher than in young adults. The annual recurrence rate for patients between 17 and 25 years of age was 3.7 per cent, a seemingly low risk; however, over a 10-year period the patient statistically had 1 chance in 3 of developing a recurrence.

Some information is available concerning the time that first recurrences of rheumatic fever occur. Comparison of the data from 2 studies[34, 35] shows considerable differences in the time the first recurrences developed (table 3). These differences may be due to multiple factors, including length of observation of the rheumatic populations, age, and number of streptococcal infections. However, the important fact is that recurrences of rheumatic

TABLE 3.—*Interval Between Initial Attack of Rheumatic Fever and First Recurrence in Patients who Experienced at Least One Recurrence*

Interval in years between first attack and first recurrence	Series of Mackie[34]		Series of Fischel[35]	
	Number	Per cent	Number	Per cent
0–1	34	24	43	37
1–2	22	15	32	28
2–3	19	13	17	15
3–4	7	5	6	5
4 or more	62	43	18	15
Total	144	100	116	100

TABLE 4.—*Major Rheumatic Recurrences Developing in Patients who have Experienced Four or More Years of Freedom from Activity** [36]

Year of observation after last rheumatic episode	Number of patients observed	Number of recurrences	Per cent recurrences
Fifth	74	12	16
Sixth	60	8	13
Seventh	48	7	15
Eighth	40	4	10
Ninth	29	0	0
Tenth	20	3	15
Eleventh	13	1	8
Twelfth	8	0	0
Total	74	35	47

* Activity is defined as chorea, objective arthritis, carditis, or nodules.

fever do occur after long periods of freedom from activity.

An earlier study of Wilson, Lingg, and Croxford[36] supports the concept that the risk of recurrence after a number of years of freedom is high. Data were presented regarding each of 412 rheumatic subjects followed for varying periods of time after their original attacks. There were 72 patients who experienced a total of 74 periods of more than 4 years of freedom from major activity. The recurrences that developed in these patients subsequent to 4 years of freedom are shown by year of observation in table 4. It is again evident that recurrences may occur many years after the original attack in spite of long intervals without rheumatic activity.

It is obvious that a rational method of management of the rheumatic patient cannot be established unless susceptibility to recurrence can be defined in relation to other factors such as age, period of freedom from activity, and the role of streptococcal infections. As mentioned previously, the decreased incidence of streptococcal infections in the adult may account for the decreased occurrence of rheumatic attacks recorded in the studies reviewed. Some information concerning the susceptibility to recurrence following an observed streptococcal infection at age 17 to 25 was obtained from an analysis of 216 patients admitted to a military hospital.* A total of 216 patients were seen who had a respiratory illness and who exhibited group A streptococci in the cultures of the oropharynx. Seventy-seven of these 216 patients received no specific treatment and were observed for signs of rheumatic activity for a minimum of 3 weeks from onset of their streptococcal infection. A diagnostic increase in the antistreptolysin titer was demonstrated in the convalescent serum as compared to the titer of the serum obtained at the onset of the respiratory illness in 71 per cent of the patients studied. Pharyngeal or tonsillar exudate was observed in 45 of the 77 patients. The attack rate for rheumatic fever in this group is recorded in table 5 according to the number of years that had elapsed since the last rheumatic episode.

TABLE 5.—*Frequency of Rheumatic Fever Recurrences in Young Adults Observed During a Streptococcal Infection**

Years since last attack of rheumatic fever	Number of infections	Recurrence of rheumatic fever					
		Definite		Possible		Total	
		Number	Per cent	Number	Per cent	Number	Per cent
0–4	15	2	13	2	13	4	27
5–9	32	6	19	1	3	7	22
10 or more	17	2	12	0	0	2	12
Unknown	13	0	0	1	8	1	8
Total	77	10	13	4	5	14	18

* No specific therapy was administered for the respiratory illness.

Rheumatic fever, according to criteria for diagnosis previously defined,[9] developed in a total of 14 or 18 per cent of the 77 patients observed during and following a streptococcal infection. The attack rate according to the number of years that had elapsed since the last rheumatic episode was 27, 22, and 12 per cent for less than 5, 5 to 9, and 10 or more years of freedom, respectively. Although the total number of cases studied was small, it is apparent that susceptibility to a recurrence following a streptococcal infection did not decrease greatly as the period of freedom from activity increased. Certainly, one should not discontinue the prophylactic regimen just because a recurrence had not been observed for a period of 5 or 10 years.*

It has been suggested that in the adult protection from recurrences might be obtained by treatment of the streptococcal infection. The data presented in table 6 show that reliance on this method is not justified. In this study, 139 patients with a past history of rheumatic fever received treatment for the respiratory illness with antibiotics and were followed for signs of recurrences. All these patients exhibited exudative tonsillitis or pharyngitis and cul-

* The authors are indebted to the professional staff of the Streptococcal Disease Laboratory for the collection of these data.

* It is possible that freedom from experience with the group A streptococcus afforded by prophylaxis for a period of 5 or more years may alter the attack rate after a proved streptococcal infection, but no data are available for analysis.

TABLE 6.—*Frequency of Rheumatic Recurrences in Young Adults Observed During a Streptococcal Infection Treated with Antibiotics*

Years since last attack of rheumatic fever	Number of infections	Recurrence of rheumatic fever					
		Definite		Possible		Total	
		Number	Per cent	Number	Per cent	Number	Per cent
0–4	35	2	6	6	17	8	23
5–9	45	2	4	2	4	4	9
10 or more	47	1	2	3	6	4	9
Unknown	12	0	0	0	0	0	0
Total	139	5	4	11	8	16	12

tures showed group A streptococci. The attack rate in this group was 3.6 per cent, but an additional 8 per cent showed some signs or symptoms of a recurrent attack. Since many streptococcal infections are inapparent, it is obvious that individuals such as those included in table 5 should be under continuous prophylaxis.

In summary, rheumatic recurrences occur in adult life in spite of freedom from activity for many years and the risk of recurrent activity in adult life following a streptococcal infection is high. Therefore, the risk of a recurrent attack of acute rheumatic fever in adults depends primarily on effective contacts with a carrier of the group A streptococcus. Thus, estimation of the risk of recurrence of rheumatic fever is an individual problem and the decision as to how long prophylaxis should be continued must be based on many factors. In the opinion of the authors, it is mandatory to continue prophylaxis as long as the patient is in school or serving in the armed services. Likewise, the adult, especially the parent, who is exposed to children should be protected. Those whose occupations demand intimate exposure to many people undoubtedly experience an increased risk. In contrast, a chauffeur-driven executive who is exposed to few people, other than his secretary and other chauffeur-driven executives, has less opportunity to contract infection. All these variable and individual factors must be considered by the physician in making the decision as to how long prophylaxis should be continued in an individual patient. It is not sufficient to rely on antibiotic treatment of a streptococcal infection, since many are inapparent or cause few symptoms and therapy does not prevent all recurrences. In addition, there is still some doubt whether therapy of the respiratory infection prevents cardiac damage. Therefore, prophylaxis should be maintained indefinitely except in those few individuals in whom the risk of contracting a streptococcal infection is negligible.

REFERENCES

[1] Commission on Acute Respiratory Diseases. A study of a food-borne epidemic of tonsillitis and pharyngitis due to B-hemolytic streptococcus, type 5. Bull. Johns Hopkins Hosp. **77:** 143, 1945.

[2] MORRIS, A. J., CHAMOVITZ, R., CATANZARO, F. J., AND RAMMELKAMP, C. H., JR.: Prevention of rheumatic fever by treatment of previous streptococcal infections. Effect of sulfadiazine. J. A. M. A. **160:** 114, 1956.

[3] MASSELL, B. F., DOW, J. W., AND JONES, T. D.: Orally administered penicillin in patients with rheumatic fever. J. A. M. A. **138:** 1030, 1948.

[4] DENNY, F. W., WANNAMAKER, L. W., BRINK, W. R., RAMMELKAMP, C. H., JR., AND CUSTER, E. A.: Prevention of rheumatic fever. Treatment of the preceding streptococcal infection. J. A. M. A. **143:** 151, 1950.

[5] Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association: Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation **11:** 317, 1955.

[6] Streptococcal Disease Laboratory: Unpublished observations.

[7] MASSELL, B. F., STURGIS, G. P., KNOBLOCK, J. D., STREEPER, R. B., HALL, T. N., AND NORCROSS, P.: Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococcic respiratory infections. J. A. M. A. **146:** 1469, 1951.

[8] BREESE, B. B.: Treatment of beta hemolytic streptococcic infections in the home. Relative value of available methods. J. A. M. A. **152:** 10, 1953.

[9] WANNAMAKER, L. W., RAMMELKAMP, C. H., JR., DENNY, F. W., BRINK, W. R., HOUSER, H. B., HAHN, E. O., AND DINGLE, J. H.: Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin. Am. J. Med. **10:** 673, 1951.

[10] HOUSER, H. B., ECKHARDT, G. C., HAHN, E. O., DENNY, F. W., WANNAMAKER, L. W., AND RAMMELKAMP, C. H., JR.: Effect of aureomycin treatment of streptococcal sore throat on the streptococcal carrier state, the immunologic

response of the host, and the incidence of acute rheumatic fever. Pediatrics **12:** 593, 1953.

[11] Catanzaro, F. J., Brock, L., Chamovitz, R., Perry, W. D., Siegel A. C., Stetson, C. A., Rammelkamp, C. H., Jr., Houser, H. B., Stolzer, B. L., Wannamaker, L. W., and Hahn, E. O.: Effect of oxytetracycline therapy of streptococcal sore throat on the incidence of acute rheumatic fever. Ann. Int. Med. **42:** 345, 1955.

[12] Weinstein, L., Boyer, N. H., and Goldfield, M.: Rheumatic fever in scarlet-fever patients treated with penicillin. A follow-up study after seven years. New England J. Med. **253:** 1, 1955.

[13] —, Bachrach, L., and Boyer, N. H.: Observations on the development of rheumatic fever and glomerulonephritis in cases of scarlet fever treated with penicillin. New England J. Med. **242:** 1002, 1950.

[14] Jones, T. D.: Diagnosis of rheumatic fever. J. A. M. A. **126:** 481, 1944.

[15] The Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association: The treatment of acute rheumatic fever in children. A cooperative clinical trial of ACTH, cortisone and aspirin. Circulation **11:** 343, 1955.

[16] Faulkner, J. M., Place, E. H., and Ohler, W. R.: The effect of scarlet fever on the heart. Am. J. M. Sc. **189:** 352, 1935.

[17] Roelsen, E.: Electrocardiographic studies in scarlet fever. Acta med. scandinav. **106:** 26, 1941.

[18] Watson, R. F., Rothbard, S., and Swift, H. F.: The relationship of postscarlatinal arthritis and carditis to rheumatic fever. J. A. M. A. **128:** 1145, 1945.

[19] Rantz, L. A., Spink, W. W., and Boisvert, P. J.: Abnormalities in the electrocardiogram following hemolytic streptococcus sore throat. Arch. Int. Med. **77:** 66, 1946.

[20] Levander-Lindgren, M.: Electrocardiographic studies in scarlet fever. Acta Paediat. Suppl. **91:** 1952.

[21] Goldfield, M., Boyer, N. H., and Weinstein, L.: Electrocardiographic changes during the course of measles. J. Pediat. **46:** 30, 1955.

[22] Hahn, E. O.: To be published.

[23] Stolzer, B. L., Houser, H. B., and Clark, E. J.: Therapeutic agents in rheumatic carditis. Comparative effects of acetylsalicylic acid, corticotropin, and cortisone. Arch. Int. Med. **95:** 677, 1955.

[24] Weinstein, L.: Personal communication.

[25] Wannamaker, L. W.: The epidemiology of streptococcal infections. *In*, Streptococcal Infections, M. McCarty, Ed., Chap. 12. New York, Columbia University Press, 1954.

[26] Rammelkamp, C. H., Jr.: Glomerulonephritis. Proc. Inst. Med. Chicago **19:** 371, 1953.

[27] —, Wannamaker, L. W., and Denny, F. W.: The epidemiology and prevention of rheumatic fever. Bull. New York Acad. Med. **28:** 321, 1952.

[28] Kaiser, A. D.: Factors that influence rheumatic disease in children. J. A. M. A. **103:** 886, 1934.

[29] Ash, R.: The first ten years of rheumatic infection in childhood. Am. Heart J. **36:** 89, 1948.

[30] Bland, E. F., and Jones, T. D.: Rheumatic fever and rheumatic heart disease. A twenty year report on 1,000 patients followed since childhood. Circulation **4:** 836, 1951.

[31] Leonard, M.: Puberty and prognosis in rheumatic fever. Am. Heart J. **14:** 192, 1937.

[32] Cohn, A. E., and Lingg, C.: The natural history of rheumatic cardiac disease: a statistical study. II. Manifestations of rheumatic activity: Recurrence, severity of infection, and prognosis. J. A. M. A. **121:** 113, 1943.

[33] Wilson, M. G., and Lubschez, R.: Recurrence rates in rheumatic fever. The evaluation of etiologic concepts and consequent preventive therapy. J. A. M. A. **126:** 477, 1944.

[34] Mackie, T. T.: Rheumatic fever. An analytical study of three hundred and ninety-three cases of rheumatic fever and eighty-nine cases of chorea. Am. J. M. Sc. **172:** 199, 1926.

[35] Fischel, E. E.: quoted by Stollerman, G. H.: The use of antibiotics for the prevention of rheumatic fever. Am. J. Med. **17:** 757, 1954.

[36] Wilson, M. G., Lingg, C., and Croxford, G.: Statistical studies bearing on problems in the classification of heart disease. III. Heart disease in children. Am. Heart J. **4:** 164, 1928.

Treatment of Rheumatic Fever

By E. G. L. Bywaters, F.R.C.P.

INCREASING knowledge of the nature of a disease often leads directly to improved preventive measures but seldom to any major advances in the treatment of the established illness. In rheumatic fever the striking advances of the last 20 years have been in the field of prevention, due to recognition of the bacterial factor and to the coincident discovery of chemotherapeutic and antibiotic agents. There has, however, been no parallel advance in the treatment of children with established rheumatic fever, which is still based on the premises enunciated in the latter part of the nineteenth century.

These premises are firstly, that the only organ seriously to be damaged during the acute phase of rheumatic fever is the heart; secondly, that this damage is due to an acute and then a chronic inflammatory granulomatous process situated in the connective tissue and on the endothelial surface of the moving parts, and thirdly, that the ultimate damage is due to fibrosis and scar formation in these sites and to mechanical shrinkage and distortion of these structures. It is presumed that the amount of scarring depends upon the amount, intensity, and duration of the inflammatory process. The first rational approach to treatment was made by Sibson, in 1877,[1] introducing rest. This followed the important lectures given by John Hilton between 1860 and 1862 on "Rest and Pain"[2]: it is noteworthy that a second edition of this book was published in 1876, 1 year before Sibson's article in Reynolds "System of Medicine." It seemed possible to Sibson, and it has seemed reasonable to almost all those who have followed after him, including the present generation, that if the work of the heart can be diminished during the time that it is diseased, the amount of inflammation and therefore the amount of inflammatory scarring might be reduced. Comparing 24 cases treated with rest with 127 cases not so rested, he found residual valve lesions in one eighth of the former and one third of the latter and no residual lesions in 71 per cent of those rested as against 47 per cent of those not rested. Although this was before the days of controlled clinical trials and there was no random allocation to establish comparability of the 2 groups or any of the other safeguards that are nowadays necessary for the comparison of treatments, few people since his time have seriously questioned this principle, and no series of children has been treated other than by bed rest. However, from time to time children are seen who have been allowed to walk around and carry on with the ordinary activities of everyday life during the early stages of this disease, since not all parents are wise enough to consult their family doctors early in the course of the disease, nor, having done so, to follow his instructions. We have seen several such patients and they have usually gone on to develop cardiac damage.

Taussig and Goldenberg, in 1941,[3] investigated a series of 84 patients classified into 3 groups according to whether (1) their hearts grew normally in size, (2) whether after initial enlargement the heart diameter stayed stationary until chest size caught up with it, resuming the usual cardiothoracic ratio, or (3) whether they showed progressive cardiac enlargement. They found 9 patients who had not been adequately rested during the acute phase: 8 of these 9 patients were in the group with progressive enlargement, which also showed a high mortality (50 per cent) and a high degree of residual valvular disease of the heart. Of the remaining 75 patients treated with bed rest, the majority showed normal cardiac growth and only 8 out of 75 showed progressive enlargement.

This prolonged bed rest is often difficult to maintain in the familiar surroundings of the child's own home and for this reason long-stay

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beds in hospitals and convalescent homes have been put aside for the purpose. In England, the London County Council started such beds in 1926 (Bach and associates, 1939[4]) as part of a comprehensive scheme to provide adequate accommodation, early diagnosis, continued education, and supervision of aftercare on both medical and social aspects. A number of these long-stay hospitals are now in existence throughout Great Britain and elsewhere and are provided with educational facilities so that development of both body and mind can proceed without undue interruption.

For practical purposes, most institutions employ graded stages of physical activity, starting with complete bed rest (stage 1) for those in the acute stages and for those with heart failure and progressing gradually until the patients are fit for departure home. While sitting up in bed involves less work for the heart than lying flat, it was found in children by experience that less incidental activity occurs (and it is this that increases the heart's work), in the flat position than when the patient is allowed to sit up. Heart failure, however, demands a sitting position. Stage 2 allows the patient to feed himself. Stage 3 is entered after the subsidence of active disease while sedimentation rate is decreasing toward normal; in this stage children are allowed to start school lessons and to wash themselves but are not allowed out of bed. Stage 4, when they are allowed increasing time out of bed, at first sitting in a chair and then walking, is not reached until all signs of clinical activity have disappeared and the sedimentation rate has been within normal limits for at least 2 weeks and usually longer, particularly if there has been clinical evidence of carditis. Thereafter the patient is gradually up-staged until he is fit to go home.

Other methods of decreasing cardiac work have from time to time been suggested, such as the use of antithyroid drugs, hypnotics such as sodium amytal, and hypotensive agents such as hexamethonium bromide. Although these drugs may reduce the work of the heart by 30 per cent in adults, (Mottu, 1954[5]) rest alone has usually been used for this purpose in children.

Criteria of Disease Activity

The duration and degree of bed rest are therefore determined by close clinical observation of the patient and by the disappearance of clinical signs of disease activity and laboratory evidence thereof. We have learned in the past few years that Aschoff bodies may survive in an apparently active form in the heart muscle sometimes for years after the subsidence of an acute attack and in the absence of any clinical or serologic signs of disease activity. Thus "disease-activity" is a matter solely of definition. For practical purposes it is generally used as meaning the presence of fever, arthritis, arthralgia, joint effusions, or changing cardiac signs. Chorea may not necessarily be associated with other clinically or serologically manifest disease activity. While erythema marginatum and the presence and persistence of nodules are usually associated with other clinical and laboratory signs of activity, on occasion they may be found to last for several months after the subsidence of the sedimentation rate to normal and the disappearance of C-reactive protein from the serum.

Perhaps the most reliable long-term clinical sign of recovery in children is the resumption of normal weight accretion, as long as the presence of accumulating edema is ruled out. We have not found that the corrected Q-T interval was very useful as an index either of activity or of carditis, despite claims to the contrary from other units and even from our own unit in its early days. It is not infrequently normal in the presence of obvious acute cardiac involvement and may remain high after the subsidence of overt signs of activity. We have not, therefore, thought it to be a useful criterion. The anemia of the acute stages, which has been characterized in the first few days (Reinhold, 1954[6]) as involving a hemolytic process with decreased survival of erythrocytes, seems to be similar to the anemia of sepsis and disappears fairly rapidly on the termination of disease activity.

The erythrocyte sedimentation rate is the most useful of all numerical indices in rheumatic activity. We take 15 mm./hour as the upper limit of normal and prefer the Westergren method to the Wintrobe or other methods, diluting with citrate, since oxalate as used in

the Wintrobe method may sometimes give falsely low readings (Goldberg, Glynn, and Bywaters, 1952[7]). The sedimentation rate depends primarily on the fibrinogen content of the plasma and is paralleled by the plasma viscosity (Lawrence, 1949[8]). It may be misleadingly low in active rheumatic fever with heart failure, as was shown by Paul Wood[9] (1936). In such instances the sedimentation rate rises to the elevated level characterizing rheumatic activity as soon as the heart failure subsides. If the erythrocyte sedimentation rate is used as an index of activity, it must be remembered that it is depressed toward normal in many cases during steroid therapy and in some during salicylates, but returns to high levels as soon as the medication has stopped.

C-reactive protein has also been found useful, since it is absent from the sera of normal patients and from that of patients convalescing from rheumatic fever. It appears rapidly in the acute phase of the disease, as also in any other acute inflammatory disease; so it is nonspecific. It is usually present, however, in congestive heart failure with activity despite a normal erythrocyte sedimentation rate. C-reactive protein disappears from the plasma usually before the sedimentation rate drops to normal levels, and we prefer to use the sedimentation rate as a guide to bed rest under normal circumstances. As a laboratory guide, other acute phase reactants, such as serum mucoprotein, glucosamine, polysaccharide, or diphenylamine color reaction offer no apparent advantages over those previously cited. The ratio of albumin to alpha-2 globulin derived from paper electrophoretic patterns may perhaps prove useful (Gilliland and Isdale, 1956[10]).

During this period of bed rest and gradual mobilization, schooling continues and reinfection with beta hemolytic streptococcus is prevented firstly by isolation of all new entrants to the ward in a sideroom, until bacteriologic nose and throat swabs are shown to be negative; secondly, by bacteriologic examination at weekly intervals of all patients and of all staff, with thorough treatment of carriers; and third, by regular daily prophylaxis with sulfadiazine 0.5 Gm. twice daily; sulfonamide prophylaxis has given very little trouble over the years; but 1 or 2 instances have occurred where transient leukopenia developed, necessitating a change to oral penicillin prophylaxis, 200,000 units crystalline penicillin G, twice a day. This gives adequate protective levels and is usually well absorbed; it is perhaps better given after than before meals, which is the usual practice (Holborow and Bywaters[11]).

For patients maintained on prophylaxis at home (and all these patients should be protected until at least the age of 18), penicillin V may be used, since it gives, for the same dosage, slightly more certain and slightly higher protection levels and does not depend on time of ingestion in relation to meals, since, being itself an acid, it is not broken down in the stomach. In the rare individual unwilling to take drugs by mouth, benzathene penicillin in a dose of 1.2 million units by intramuscular injection will provide protective levels for several weeks but this is not practical for long-term treatment and is often painful. For patients convalescent from rheumatic fever we prefer routine oral prophylaxis to the early treatment of streptococcal sore throats by penicillin, since the latter is not always to be relied upon and leaves more to mischance. Children should also be treated with penicillin during dental extractions, tonsillectomy, etc., since, although subacute bacterial endocarditis is rare in childhood, we have seen it develop at the age of 14.

Curative and Suppressive Agents

No drug is yet known that cures this disease as arsphenamine and penicillin "cure" syphilis, in the sense of cutting it short. However, in addition to the above regime of general care, most patients with rheumatic fever today receive either hormones or salicylates or both. These and similar substances appear to act at particular levels of the reacting mechanism, suppressing therefore some of the manifestations of the disease. If the suppression were complete and capable of being maintained and the underlying pathologic process were self limited, this would amount to a cure. Unfortunately the suppression appears to be incomplete. Regardless of drug or dosage level and in all published series, some patients con-

tinue to develop signs of carditis and lasting murmurs even when seen and treated within a fortnight of the onset of the disease with neither clinical nor historical evidence of a previous attack. Some patients still die. Certain cases develop carditis, failure, or nodules during treatment with either salicylates or hormones. However, both with massive salicylate therapy and with steroids, some observers have claimed a worthwhile suppression of carditis compared with ordinary low salicylate dosage, although there is no unanimity on this score.

The most valuable result of modern work in the therapeutic field is the recognition that clinical trials must be very strictly controlled if they are to give meaningful answers, and that the answers they give apply only to the questions that were asked. The major study in this field is the joint United Kingdom-United States cooperative study of cortisone, ACTH, and aspirin published in this journal in 1955.[12] This report detailed the course of the disease in a total of 497 children over a 6-week period of treatment, periods of retreatment if necessary, and the remainder of a period up to 61 weeks from the start of treatment. Results showed no uniform superiority of 1 treatment over another in regard to all the manifestations of the disease. At the end of the year there was no significant difference between the 3 treatment groups in the status of the heart.

This study established a standard for therapeutic evaluation in this field as had similar controlled cooperative studies in the evaluation of hormones for the treatment of rheumatoid arthritis (Medical Research Council-Nuffield Foundation Report, 1954[13]). It is probable that further studies to establish therapeutic usefulness, although differing largely perhaps in design, will have to conform to the principles underlying such planned studies. In particular, for any dosage plan patients must be selected in a random way and care must be taken to ensure comparability between the treated groups in all important characteristics before the start of treatment.

A parallel study in 128 adults with the same dosage (Stolzer, Houser and Clark, 1955,[14] and Houser and associates (1954[15]) gave similar results in the acute stage and did not permit a conclusion that cortisone and ACTH were superior to aspirin in the prevention of valvular disease. However, significantly fewer new murmurs appeared in the cortisone group during therapy and fewer murmurs that were considered "significant" were found in this group at the end of 14 months (although this latter difference achieved a probability of only 0.11).

It may be that a higher or longer dosage would give different results: a further trial at Taplow in 30 first-attack cases seen and treated within a fortnight of the onset, with 12 weeks' treatment with cortisone or salicylate at a similar dosage level has shown residual cardiac signs after a year of observation in 7 of each treatment group. Others have used higher dosage levels but with conflicting results. Thus Wilson and Lim (1956)[16] continue to be enthusiastic about the results of steroids at 320–400 mg./day for an average period of 7 days starting between 3 and 21 days from the onset of the disease: Done and co-workers (1955)[17] found fewer residual murmurs in 46 hormone-treated cases (up to 300 mg./day of cortisone) than in 34 treated with salicylates or bed rest. Harris' group, (1956)[18] on the other hand found no significant difference between 50 hormone-treated patients (dosage 300 mg./day for adults and proportionately less for children) and 50 controls treated with salicylates in low doses in regard to murmurs during the hospital course. In a small but well set-up trial comparing massive salicylate plus cortisone, massive salicylate, and low salicylate dosage alone, Holt and associates (1954)[19] demonstrated a more rapid fall of erythrocyte sedimentation rate in the first group. One child, however, died of heart failure on the fifteenth day of her first attack after 10 days of treatment. They remarked on the difficulties and toxic complications (Holt, 1954[20]) of the combined treatment, but believed this combination to be worth further exploration.

Massive salicylate therapy alone (i.e., achieving blood levels between 30–40 mg. per cent) has also had its protagonists ever since 1943 when it was first introduced by Coburn; the most recent appraisal (Illingworth and associates, 1954[21]) included a critical survey of all

previous work and was carefully planned. The slight advantage shown in the salicylate-treated cases in regard to changes in murmurs over those treated with bed rest alone was not statistically significant after more than 1 year's observation, although the erythrocyte sedimentation rate had shown a more rapid fall in the treated group.

Other phenolic compounds have also been studied: phenylbutazone, gamma resorcylate (Reid and associates, 1951[22]), 3 OH-2 phenylcinchonine acid, (Clark and Houser, 1953[23]) and sodium gentisate (Clarke, Mosher, and Clarke, 1953[24]) but, broadly speaking, the observers may be grouped as those with enthusiasm and no controls and those with controls but no enthusiasm. None of these substances offers a clear advantage over aspirin.

It is therefore still far from clear whether salicylate, steroid, a combination thereof, or bed rest alone offers the best chance of escaping residual valvular deformity and even less clear what is the best dosage level to employ. Nevertheless, it appears certain that both hormones and salicylates suppress certain features of the acute phase, mitigate the severity of the disease, and make the ill patient feel considerably easier, particularly in regard to fever and joint manifestations. In high and prolonged dosage both hormones and salicylates induce dangerous, rarely even fatal reactions. The incidence and severity of these reactions can be diminished by careful observation of the patient and prompt action: thus with salicylates the most dangerous signs are hemorrhage and hyperpnea and perhaps pulmonary edema (Sutcliffe, 1955[25]). Because of the salt and water-retaining properties of cortisone we tended to use aspirin in children with heart failure. Although now with the delta analogues higher effective doses may be given without this complication, another danger has taken its place, at least in adults and teenagers—gastric erosion. We routinely give antacids with these substances. Adjuvant therapy, such as digitalis, digoxin, mersalyl, is, of course, given when required.

Long-Term Supervision

Finally, it should be borne in mind that the treatment of patients with rheumatic fever is a long-term operation involving careful supervision of the child not only in hospital during the acute phase but at home and in school, during the rest of childhood and perhaps beyond. To this end, centers that are concerned with this problem conduct follow-up and supervisory clinics to maintain contact with the patient and his family at regular intervals following recovery from the acute illness. A social service worker is essential for the successful operation of this long-term service, which may include help and guidance for the family as a whole, as well as advice on schooling and employment for the patient. Liaison is maintained with the family doctor, the local consultant, and with the school medical officer. We usually see the child 3 times in the first year after the acute attack and thereafter at 6 monthly or yearly intervals, paying particular attention not only to the clinical, particularly the cardiac status and the amount of exercise that the child can undertake, but also to the maintenance of prophylaxis and its efficacy. Routine checks are made of hemoglobin, sedimentation rate, antistreptolysin titer, and for sulfonamide derivatives in the urine by La Rosa's (1945)[26] test paper if sulfonamide prophylaxis is used. Unfortunately, this test does not pick out those who are conscientious only on the day of their follow-up!

Summary

The treatment of active rheumatic fever has changed little over the course of years; bed rest is believed to be necessary for the lessening of residua although there is only slight evidence for this belief. The virtues of salicylates in high and low dosage and of similar compounds, of corticotropin, cortisone and its analogues continue to be discussed but chiefly now in the light of those studies that are well designed and include adequate control observations. There is still some hope that a drug in the steroid or salicylate class might be found that would make suppression worth while. What is really wanted is something that will inhibit the consequences of streptococcal infection at the stage of rheumatic fever in a more basic way. Achieving this goal depends upon knowing more about the etiologic mechanisms involved.

REFERENCES

[1] Sibson, F.: *In*, Reynold's System of Medicine, Vol. 4. London, MacMillan, 1877, p. 526.

[2] Hilton J.: Rest and Pain. London, Bell, 1877.

[3] Taussig, H. B., and Goldenberg, M.: Roentgenologic studies of size of heart in childhood; 3 different types of teleroentgenographic changes which occur in acute rheumatic fever. Am. Heart J. **21:** 440, 1941.

[4] Bach, F., Hill, N. G., Preston, T. W., and Thornton, C. E.: Juvenile rheumatism in London. Ann. Rheumat. Dis. **1:** 210, 1933.

[5] Mottu, T.: Artificial reduction of the heart effort. The effect of the association of hexamethonium bromide and sodium amytal. Am. Heart J. **47:** 270, 1954.

[6] Reinhold, J. D. R.: The survival of transfused cells in acute rheumatic fever, with reference to a latent hemolytic mechanism. Arch. Dis. Childhood **29:** 201, 1954.

[7] Goldberg, S., Glynn, L. E., and Bywaters, E. G. L.: Anomaly of sedimentation rate in rheumatic diseases. Brit. M. J. **1:** 202, 1952.

[8] Lawrence, J. S.: Plasma viscosity. Ann. Rheumat. Dis. **8:** 209, 1949.

[9] Wood, P.: Erythrocyte sedimentation rate in diseases of heart. Quart. J. Med. **5:** 1, 1936.

[10] Gilliland, I., and Isdale, I. C.: Unpublished data.

[11] Holborow, E. J., and Bywaters, E. G. L.: Unpublished data.

[12] United Kingdom-United States Joint Report on Rheumatic Fever: The treatment of acute rheumatic fever in children. A cooperative clinical trial of ACTH, cortisone and aspirin. Circulation **11:** 343, 1955.

[13] Medical Research Council-Nuffield Foundation Report. Brit. M. J. **1:** 1223, 1954.

[14] Stolzer, B. L., Houser, H. B., and Clark, E. J.: Therapeutic agents in rheumatic carditis. Comparative effects of acetylsalicylic acid, corticotropin and cortisone. Arch. Int. Med. **95:** 677, 1955.

[15] Houser, H. B., Clark, E. J., and Stolzer, B. L.: Comparative effects of aspirin, ACTH and cortisone on the acute course of rheumatic fever in young adult males. Am. J. Med. **16:** 168, 1954.

[16] Wilson, M. G., and Lim, W. N.: Natural course of active rheumatic carditis and evaluation of hormone therapy. J. A. M. A. **160:** 1457, 1956.

[17] Done, A. K., Ely, R. S., Ainger, L. E., Rodman Seeley, J., and Kelley, V. C.: Therapy of acute rheumatic fever. Pediatrics **15:** 522, 1955.

[18] Harris, T. N., Friedman, S., Needleman, H. L., and Saltzman, H. A.: Therapeutic effects of ACTH and cortisone in rheumatic fever: Cardiologic observations in a controlled series of 100 cases. Pediatrics **17:** 11, 1956.

[19] Holt, K. S., Illingworth, R. S., Lorber, J., and Rendle-Short, J.: Cortisone and salicylates in rheumatic fever. Lancet **2:** 1144, 1954.

[20] —: Salicylates in rheumatic fever. Difficulties experienced in treating children with large doses. Lancet **2:** 1197, 1954.

[21] Illingworth, R. S., Burke, J., Doxiadis, S. A., Lorber, J., Philpott, M. G., and Stone, D. G. H.: Salicylates in rheumatic fever: An attempt to assess their value. Quart. J. Med. **23:** 177, 1954.

[22] Reid, J., Watson, R. D., Cochran, J. B., and Sproull, D. H.: Sodium γ-resorcylate in rheumatic fever. Brit. M. J. **2:** 321, 1951.

[23] Clark, E. J., and Houser, H. B.: Comparative effects of 3-hydroxy-2-phenylcinchoninic acid (HPC) and aspirin on acute course of rheumatic fever and occurrence of rheumatic valvular disease. Am. Heart J. **45:** 576, 1953.

[24] —, Mosher, R. E., and Clarke, C. N.: Phenolic compounds in the treatment of rheumatic fever. I. A study of gentisic acid derivatives. Circulation **7:** 247, 1953.

[25] Sutcliffe, J.: Pulmonary oedema due to salicylates with report of a case. Brit. J. Radiol. **28:** 314, 1955.

[26] La Rosa, W. V.: Use of test paper for rapid estimation of sulfonamides in blood and other body fluids. J. Lab. & Clin. Med. **30:** 551, 1945.

CLINICAL PROGRESS

Coronary Embolism

By E. Lee Shrader, M.D., M. B. Bawell, M.D., and V. Moragues, M.D.

THE clinical diagnosis of coronary embolism has been made and reported 4 times in the literature. One case was reported by Hamman[1] in 1941 of a 34-year-old woman who suddenly developed symptoms of heart failure following an acute respiratory infection. She had no previous history or evidence of heart disease and failed to show any residual evidence or symptoms of heart disease. He reasoned quite logically that she must have had some acute embolic accident, temporarily impairing the function of her heart, and thought that the lungs had been the source of the embolus. Since the patient survived, there was no postmortem examination to support the correctness of Hamman's reasoning. He thought that the lungs, because of the frequency with which they are infected, should be a fruitful source of emboli to the coronary arteries. Actually, a survey of the reported cases reveals only 2 other cases in which the source of the embolus was due to an infectious process in the lungs. The rarity of this chain of events detracts from, rather than supports the diagnosis of coronary embolism in his case.

Mussafia,[2] in 1948 reported a case thought to be coronary embolism in a 24-year-old white woman with rheumatic heart disease and bacterial endocarditis. On the fourth day of treatment she developed violent retrosternal pain, which persisted for 2 days despite morphine. The electrocardiogram was that of an infarct of the anterior wall of the left ventricle. The patient survived the acute attack and was still alive and under observation a year later.

The third case, reported by Glushien, Reiter, and Fischer[3] in 1952, was a 24-year-old man with diabetes, necrotizing renal papillitis, and acute bacterial endocarditis of the aortic valve. The clinical diagnosis was made 2 days before death and confirmed by autopsy. The right coronary artery was occluded by a vegetation from the aortic valve.

The fourth case diagnosed clinically was reported in 1953 by Cheng, Cahill, and Foley.[4] Their case was a 21-year-old white woman with mitral stenosis; the source of the embolus was a thrombus in the left atrium and was confirmed by autopsy.

Thus, from the literature, we have 4 cases of coronary embolism that were diagnosed ante mortem. Two were proved by autopsy; the other 2 survived, and the diagnosis is therefore presumptive in them.

Textbooks of medicine rarely list coronary embolism in their indices. White[5] in his "Diseases of the Heart" dismissed it with a 4-line statement as follows, "The coronary arteries, healthy or relatively healthy themselves, may rarely be blocked by emboli, even of air, so that death or cardiac infarction may result, or they may be more or less occluded at their mouths by syphilitic aortitis or by aortic valve vegetations in bacterial endocarditis." This statement, factually correct, does not give a clear understanding of the clinical entity of coronary embolism. Yet it is the only statement found in 5 textbooks, 4 of which are devoted to heart disease.

Pathologically, the diagnosis was first made by Virchow[6] in 1856. The description of his case gives the age and sex of the patient and the source of the embolus. He also stated that several coronary arteries were obstructed by emboli. He did not mention which arteries were involved, the state of the myocardium, nor the pathologic condition of the arterial walls. Since Virchow reported this case, other instances have been reported more and more frequently.

In 1926, Karsner[7] denied the pathologic validity of a case of coronary embolus unless the source of the embolus was clearly indicated. He did not believe that a thrombus and an embolus could be histologically differentiated unless the arterial wall at the site of the occlusion was healthy. But even though this were

apparent, he insisted that the case should not be accepted as proved, unless the source of the embolus was also clearly demonstrated. Saphir,[8] in 1933, and Garvin and Work,[9] in 1939, concurred in Karsner's criterion for the acceptance of a case as a proved one and added that most cases of coronary embolism died suddenly. They implied that sudden death should be considered presumptive evidence of coronary embolism.

Saphir,[8] in his 1933 review of the literature, found 40 reported cases of coronary embolism. He considered that 29 of these could not be accepted as proved cases. The remaining 11 he reviewed, giving the age and sex of the patient, the source of the embolus, the coronary artery involved, and the types of death. To this group, he added 3 more cases of his own. He obviously found it difficult to set up any rigid criterion for judging the validity of a case, for he commented on Marie's[10] statement, in 1897, that Virchow's case was the only proved one. He implied that this seems to be "too extreme" a position, and yet he admitted "several" reports are not convincing.

Since Saphir's[8] survey in 1933, 38 other cases have been reported, making a total of 81. Some of them cannot be considered in this clinical review for obvious reasons. For instance, Kirschbaum,[11] in 1936, in a pathologic study of 612 cases of coronary disease found in 6,754 routine autopsies, stated that 4 were due to coronary embolism. He gave no clinical data nor did he state the coronary vessel involved. Similarly, in 1935, Applebaum and Nicolson[12] found 4 cases in 168 cases of coronary disease studied pathologically. They gave no clinical data, but they did indicate that the left coronary artery was involved 3 times and the right 1 time. This greater involvement of the left rather than the right coronary artery is in agreement with the facts found in this survey of the literature. We have been unable to obtain the articles in which Greenstein,[13] in 1943, and Ramos, LeVaci, and Fonseca,[14] in 1946, reported cases. In 1882, Huber[15] reported 3 cases but gave no clinical data. In 1925, Benson and Hunter[16] reported 14 cases of myocardial infarction believed to be due to coronary embolism, but also did not give any clinical data. There are, therefore, 27 cases reported with inadequately detailed clinical or pathologic data for the purposes of this discussion.

The clinical and pathologic data in the reports of the remaining 54 cases serve as the basis for our presentation and analyses of the clinical entity, coronary embolism. In these 54 selected cases, there have been omissions of data that would be helpful in evaluating the total group of reported cases. Frequently facts, such as the age and sex of the patient, the nature of the embolus, and the artery involved, are not stated in the reports.

Because of these omissions the total number of cases in the various categories chosen for analyses vary. This variation in data, however, is slight and does not appreciably alter the clinical picture constructed by this analysis of the reported cases. In analyzing these selected cases we have chosen the following categories: age, sex, source of embolism, the artery involved, the state of myocardium, the type of death, and the mortality rate.

Age

Age seems to be extremely significant and has been checked in a variety of ways. Of these cases, the age was stated in 49, and the range was from 10 to 70 years, with an average of 39. If these cases are catalogued by decades, 19 are in the range of 31 to 40. Ten cases occur in the next younger age group of 21 to 30, and 11 occur in the next older age group of 41 to 50. The remainder occur as shown in table 1. Forty-two of the 49 cases had a coronary embolism within the age limit of 20 to 50, with emphasis on the 31 to 40 age range.

Sex

In 47 of the cases the sex was stated. Thirty-five were male and 12 were female.

Artery Occluded

In 51 cases the artery occluded was noted. The left coronary and its various branches were

Table 1.—*Age Incidence by Decades*

Age	10–20	21–30	31–40	41–50	51–60	61–70	71 and over
Number of cases	2	10	10	11	3	2	2

nvolved 36 times: 17 of them involved the left lescending branch, 2 the circumflex, and 3 each he circumflex and anterior descending branch. The right coronary and its branches were involved 7 times: 6 were of the right main coronary, and 1 in one of its branches. The right and left main coronaries both were involved 4 times. In 1 case the main right and descending left were occluded.

When the age was plotted against the arteries involved, it was found that the majority of cases involving the left coronary arteries occurred between the ages of 20 and 50, with approximately one-half between 30 and 40.

As to sex, we have the same general correlation. In the 12 females the left coronary artery or its branches were involved 6 times, and the right coronary once. Both were involved once, and in 4 the artery was not named.

In the 35 male cases, the left coronary artery or its branches were involved 21 times, the right or its branches 5 times, both 3 times, and in 6 cases the location was not specified.

Source of the Embolism

In reference to the source of the embolus, there are complete data in 54 cases. In 22 cases, the source of the embolus was stated to be an endocarditis, either acute, subacute, or chronic, and in some cases unspecified. Seventeen of these cases were said to be due to either acute or subacute bacterial endocarditis involving the mitral or aortic valves (mitral 3, aortic 9, aortic and mitral 3, unspecified 2); 1 was chronic bacterial endocarditis, and the involved valve was unspecified; there are 4 cases in which the nature of the endocarditis was not specified. In 3 of these 4 cases the valves involved were not specified, and in 1 it was the mitral valve. In 28 cases, the source of the embolus was stated to be a thrombus. In 6 of these 28, the thrombus was on 1 or both ventricular walls, and in 14 it was on the first portion of the aortic wall, aortic valve, or the left atrial wall. In 3, the thrombus was in the main coronary artery (1 right and 2 left). In 4, it was in the veins of the pelvis and reached the left side of the heart through a patent foramen ovale (paradoxical). In 1, it was thought to have occurred from an abcess in the lung, and in another from an acute pulmonary infection.

Table 2.—*Source of the Embolus*

Bacterial vegetations	Thrombi mural and first portion aorta	Thrombus main coronary artery	Paradoxical embolism (extremities)	Lungs	Calcified heart valve
21 cases	20 cases	3 cases	4 cases	2 cases	1 case

Table 3.—*Sudden Deaths by Age Groups*

10–20	21–30	31–40	41–50	51–60	61–70	71 and over
1	4	11	0	0	1	2

There are 3 other types of embolic phenomena that deserve special mention. One was a mass of caseous material found in a main coronary artery in a patient with advanced tuberculosis. Microscopic sections of this embolus showed many tubercle bacilli. Another was a calcareous mass occluding the left main coronary artery for which no source was reported. The third was a very unusual case, previously reported by the authors,[17] of a calcific mass that became detached from a calcified aortic valve.

State of the Myocardium

After 1933 the reports of cases in the literature were more complete. Prior to 1933, no reports gave any information about pathology involving the myocardium. We collected 23 subsequent cases in which the myocardium was described. In 15 there was an infarction of the ventricle, and 1 had a rupture of the right ventricle. In 4 cases diffuse fibrosis or scarring of the ventricular muscle was noted. In 4 cases the ventricle was stated to be normal.

Type of Death and Mortality Rate

The last category in this analysis involves the type of death and mortality. Twenty-three of the cases died suddenly, 21 died gradually, and in 8 the type of death was not specified. Among the 23 cases dying suddenly, myocardial infarctions were noted 4 times. Among those cases in which death occurred gradually, infarctions were noted 12 times. There were no infarctions in which the type of death was not specified.

The mortality rate was high, approximately 96 per cent.

Discussion

A comparison of these cases with those of coronary thrombosis is of interest. The age pattern in coronary embolism is at least 2 to 3 decades younger than in coronary thrombosis. In both groups the arteries involved are usually the same. Schlesinger and Zoll[18] found that the descending branch of the left coronary artery, the left circumflex artery, and the right coronary artery were all equally involved. It is thus apparent that the left coronary artery and its left branches (left descending and left circumflex) are involved twice as often as the right coronary artery. The type of death varied in each group. In coronary embolism it occurred suddenly in about 50 per cent of the cases. This is not so in the initial attack of myocardial infarction from coronary thrombosis. Furthermore, myocardial infarction from coronary embolism is almost invariably fatal, whereas a large percentage of patients recover from the myocardial infarction from coronary thrombosis, with a more or less satisfactory state of health. This is, however, what one would expect, for the sudden occurrence of a myocardial infarction due to an embolus does not permit time for the development of new collateral circulation. In myocardial infarction resulting from coronary thrombosis the process is a slowly developing one of atherosclerosis and thus the coronary circulation has time to develop collateral anastomosis.

Table 4.—*Gradual Deaths by Age Groups*

10–20	21–30	31–40	41–50	51–60	61–70	71 and over
0	4	4	4	4	1	0

Table 5.—*Comparative Data on Coronary Embolism and Thrombosis*

	Embolism	Thrombosis
Sex	Male predominates	Male predominates
Site of occlusion	Left coronary distribution	Left coronary distribution
Etiology	Bacterial endocarditis; thrombi intra- and extracardiac, "calcific material" etc.	Atherosclerosis of coronary arteries
Previous cardiac or arterial damage	Rheumatic fever; syphilitic aortitis; bacterial endocarditis	Rarely (except coronary thrombosis)
Exitus	Sudden in approximately 50 per cent	May be sudden but not usually
Mortality rate	96 per cent	15–25 per cent

In coronary embolism there is usually some preceding cardiac damage or pathology, in the form of endocarditis or thrombi from previous damage to some part of the heart, such as the ventricular walls or a sclerotic artery. In a few cases the embolus arises in distant parts of the body and reaches the left side of the heart through a patent foramen ovale. In contrast, coronary thrombosis occurs in numerous cases without any preceding cardiac disease or damage. The rarity of coronary embolism and its predilection for the left coronary arterial tree make possible its confusion with coronary thrombosis, especially if no autopsy is performed. One of the criteria previously discussed for a diagnosis of an embolism in a coronary artery was an adequate autopsy revealing a normal arterial wall at the site of the occlusion.

The future of coronary embolism seems worthy of discussion. Two of the most common preceding diseases that had injured the heart in the reported cases were syphilitic heart disease and rheumatic heart disease or complications of them. The effective and adequate treatment of syphilis over the past few decades has made syphilitic heart disease a rarity in this country. No case of coronary embolism resulting from syphilitic heart disease has been reported in the past 10 years. With the use of antibiotics bacterial endocarditis is less frequent and, when diagnosed, is in most cases curable. With the use of antibiotics for the prevention of rheumatic fever, rheumatic heart disease should become less frequent. It is interesting that in only 1 case did a thrombus arise in the atria.

The frequency with which myocardial occlusion occurs from embolism in the left anterior descending branch and the left circumflex is of interest. This parallels, in general, the occurrence of myocardial infarction from a

coronary thrombus. There seems no adequate explanation for the similarity of the site of the occurrence of myocardial infarction from both coronary embolism and coronary thrombosis at the present time. It is a topic for further study by the authors. The higher incidence of syphilis and bacterial endocarditis in men may lead to the same sex incidence in coronary embolism, since these 2 conditions form the largest group of preceding heart disease in coronary embolism.

Sudden death in young persons with thrombophlebitis of the lower extremities or the pelvis but otherwise healthy, should raise the possibility of a paradoxical coronary embolism through a patent foreamen ovale.

There is no treatment for coronary embolism except the treatment of the underlying causes. With the better treatment of rheumatic heart disease, bacterial endocarditis, and syphilitic heart disease, coronary embolism may become a much rarer condition in the future.

Summary

Data were selected in a review of the literature from about 54 cases of coronary embolism. A majority of the cases were men between 30 and 40 years of age. The sources of the emboli were chiefly vegetations from bacterial endocarditis and cardiac thrombi from pre-existent heart disease. These 2 sources accounted for the majority of the emboli. The left coronary artery was involved most frequently, and the type of death was usually sudden. Coronary emboli almost always produce death. A comparison of the various factors involved in coronary emboli has been made with coronary thrombosis.

Summario in Interlingua

Es presentato datos seligite ab un revista del litteratura relative a circa 54 casos de embolismo coronari. In le majoritate del casos le patientes esseva homines de etates de inter 30 e 40 annos. Le origine del embolos esseva principalmente in vegetationes ab endocarditis bacterial e in thrombos cardiac ab pre-existente morbo cardiac. Le arteria coronari sinistre esseva involvite le plus frequentemente, e le typo de morte esseva generalmente subitanee. Embolos coronari resulta quasi semper in le morte del patiente. Esseva interprendite un comparation inter le varie factores involvite in embolos coronari e thromboses coronari.

REFERENCES

[1] Hamman, L.: Coronary embolism. Am. Heart J. **21:** 401, 1941.

[2] Mussafia, A.: Embolia coronaria in corso di endocardite batterica subacute. Cuore e circolaz **32:** 91, 1948.

[3] Glushien, A. S., Reiter, M. D., and Fischer, H.: Coronary embolism (intra vitam diagnosis) and necrotizing renal papillitis: Case report. Ann. Int. Med. **36:** 679, 1952.

[4] Cheng, J. T. O., Cahill, W. J., and Foley, E. F.: Coronary embolism J. A. M. A. **153:** 211, 1953.

[5] White, P. D.: Diseases of the Heart. Ed. 3. New York, Macmillan, 1946.

[6] Virchow, R.: Ueber capilläre Embolie. Virchows Arch. path. Anat. **9:** 307, 1856.

[7] Karsner, H. T.: Human Pathology. Philadelphia & London, J. B. Lippincott, Co., 1926.

[8] Saphir, O.: Coronary embolism. Am. Heart J. **8:** 312, 1933.

[9] Garvin, C. F., and Work, J. L.: Coronary embolism. Report of three cases. Am. Heart J. **18:** 747, 1939.

[10] Marie, R.: L'infarctus du myocarde, thése pour le doctorat en médicine. Paris, G. Carre, et C. Naud, c. 1897.

[11] Kirschbaum, J. D.: Statistical study of coronary disease. A review of 6,754 necropsies. Illinois M. J. **69:** 150, 1936.

[12] Applebaum, E., and Nicolson, G. H. B.: Occlusive diseases of the coronary arteries. Am. Heart J. **10:** 662, 1935.

[13] Greenstein, J.: Thrombus formation in first part of aorta and coronary embolism; its medico-legal aspects. South African M. J. **17:** 103, 1943.

[14] Ramos, J. LeVaci, I. D., and Fonseca, L. C.: Embolia, coronaria (sobre un caso, com verific acao necroscopica) Hospital Rio de Janiero **29:** 933, 1946.

[15] Huber, K.: Ueber den einfluss der Kranzarterienerkrankungen auf das Herz und die chronische Myocarditis. Virchows Arch. path. Anat. **89:** 236, 1882.

[16] Benson, R. L., and Hunter, W. C.: Pathology of coronary arterial disease. Northwest Med. **24:** 606, 1925.

[17] Moragues, V., Bawell, M. B., and Shrader, E. L.: Coronary embolism: review of literature and report of a unique case. Circulation **2:** 434, 1950.

[18] Schlesinger, M. J., and Zoll, P. M.: Incidence and localization of coronary artery occlusions. Arch. Path. **32:** 178, 1941.

ABSTRACTS

PATHOLOGIC PHYSIOLOGY

Martini, L., and Rovati, V.: Posthypophyseal Involvement in Epinephrine Antidiuretic Action. Arch. pharmacodyn. **114:** 365 (Jan.), 1956.

Epinephrine has often been considered as the humoral agent stimulating the release of adrenotropic hormone from the hypophysis after stressful stimuli. It has also been suggested that under the same conditions posterior pituitary hormones are released into the blood and reach the anterior lobe, which is then stimulated. The experiments of the authors bring new evidence that epinephrine causes a conspicuous discharge of antidiuretic hormone.

The experiments were performed on dogs and rats. The unanesthetized dogs after hydration were given epinephrine intravenously or intrathecally in the amount of 2 to 40 μg./Kg. Urine flow was expressed in ml./min. Adult albino rats were used; some of them served as controls, others were hypophysectomized. In normal dogs a dose of 15 to 30 μg./Kg. of epinephrine caused antidiuresis and hypertension, the latter lasting much shorter than the former. Two μg./Kg. intrathecally in normal dogs caused a long lasting antidiuretic action without change of blood pressure. This effect is present after denervation of the kidneys. In normal rats 50 μg./Kg. of epinephrine intraperitoneally produces a marked antidiuresis which is absent in hypophysectomized rats. According to the authors these experiments suggest that the effect of epinephrine on the anterior pituitary gland may be mediated by the humoral action of the hypothalamic-posthypophyseal system.

SCHERF

Mudge, G. H., and Hardin, B.: Response to Mercurial Diuretics During Alkalosis: A Comparison of Acute Metabolic and Chronic Hypokalemic Alkalosis in the Dog. J. Clin. Invest. **35:** 155 (Feb.), 1956.

The effects of mercurial diuretics are susceptible to changes in acid-base balance. To study the mechanisms involved dogs were made acutely alkalotic by the infusion of sodium bicarbonate. A refractoriness to mercurials was noted. However, when alkalosis of a similar degree was produced by potassium depletion the diuresis was normal or increased. It would appear that factors other than the filtered chloride load determine the effectiveness of mercurial diuretics. The authors think it likely that tubular pH plays an important role. An increase in the acidity of the tubular cells may facilitate the interaction of a cellular constituent and the mercurial.

WAIFE

Gilmore, J. P., and Hardford, S. W.: Hemodynamic Response of the Dog to Thermal Radiation. J. Appl. Physiol. **8:** 393 (Jan.), 1956.

Although there are many reports in the literature describing the histopathologic effects of thermal injury, there are few reports describing the circulatory responses. In view of this, the present study was initiated in order to define some of the hemodynamic responses to thermal radiation.

The parameters measured were cardiac output by the dye injection technic, arterial pressure, right atrial pressure, plasma volume by the T-1824 technic, hematocrit, blood volume, heart rate, and plasma proteins. After control determinations, shaved areas of anesthetized dogs were exposed to a burn apparatus for varying periods of time (average 70 sec.) to give a 30 per cent surface area burn. Following the burning, determinations were made at ¼, 1, 3, 6, and 12 hours. All dogs were autopsied and histologic studies made.

Third degree burns were produced in this way. Thermal radiation decreased mean arterial blood

pressure (24 mm. Hg) at 15 min. After this the pressure rose until the sixth hour and then gradually fell to the 15 min. post-burn level. There was no significant change in right atrial pressure until 3 hours post-burn when a gradual inconsistent decline started and continued. Heart rate decreased at 15 min., but increased above control levels thereafter. Thermal radiation decreased cardiac output to 45 per cent of the control at 15 min., 37 per cent at 1 hour, and 21 per cent at 12 hours. Hematocrit increased 15 per cent above the control at 15 min. and a maximum of 50 per cent at 12 hours. Hemolysis was observed, so that hematocrit was probably not a true measure of hemoconcentration. Plasma volume was lowered 19 per cent at 15 min., 27 per cent at 6 hours, and 37 per cent at 12 hours. There were no consistent changes in plasma proteins. Albuminuria and hematuria were found. Hyperthermia, reaching a maximum 12 hours after burning, occurred in most dogs. All animals died from 6 to 21 hours after burning. Death usually occurred precipitously. Control studies without burns were accomplished and failed to produce the changes noted above.

Hemodynamic responses of 14 dogs to a severe third degree 30 per cent surface area burn are described. Plasma volume loss is not the initiating factor of burn shock and the possibility of a toxin as this initiating factor is discussed.

WECHSLER

Aviado, D. M., Jr., Cerletti, A., Li, T. H., and Schmidt, C. F.: The Activation of Carotid Sinus Pressoreceptors and Intracranial Receptors by Veratridine and Potassium. J. Pharmacol. & Exper. Therap. **115:** 329 (Nov.), 1955.

Attempts to activate the Bezold-Jarisch reflex (bradycardia, vasodilatation and apnea) with anything other than foreign chemicals have proved unsuccessful. One must therefore conclude either that the responsible nerve elements are normally activated by unknown chemical agents or that they are not a true chemoreceptor system but are only the manifestation of an accidental stimulation of normal pressoreceptors by certain foreign chemicals. The latter view is not compatible with the fact that veratridine, 1 of the most potent stimulators of the Bezold-Jarisch reflex, did not affect 1 of the most sensitive known baroreceptors, the carotid sinus. The present study was undertaken to explore the possibility that this result occurred because of the peculiarities in the blood supply of the carotid baroreceptors. Another point of some interest was the explanation for the occasional occurrence of vasodilatation after intracarotid injection of veratridine following section of Hering's nerve.

Respiration, femoral blood pressure and heart rate were recorded in anesthetized dogs. The aortic depressor nerves were cut. Carotid pressodenervation (by cutting fibers between carotid sinus and carotid body) and additional chemodenervation (by cutting Hering's nerve) were accomplished. Injections were made into the following (a) cannula in femoral vein, (b) plastic catheter inserted through external jugular into the right atrium, (c) plastic catheter through a parietal burr hole into the extradural space, (d) cannulated vertebral artery supplied continuously with blood from a femoral artery, (e) needle cannula in central end of superior thyroid artery, and (f) needle cannula into lingual artery.

The results obtained in these studies confirm the ability of veratridine to activate the pressoreceptors of the carotid sinus. The inability of veratridine to elicit a response, when administered into the lumen of the carotid sinus, can now be explained on the nature of the blood supply to the pressoreceptors. Two intracranial reactive areas have been demonstrated, a stimulatory area, probably medulla accessible to vertebral and intracisternal injections and an inhibitory area, probably meningeal receptor, accessible to occipital artery and extradural injections. Both areas can affect respiration, heart rate, and arterial blood pressure. The fact that veratridine can activate pressoreceptors in the carotid sinus lends support to the belief that the drug reflexes (Bezold-Jarisch reflexes) from the heart and lungs are arising from previously described cardiopulmonary pressoreceptors.

WECHSLER

PHARMACOLOGY

Deal, C. P., Jr., and Green, H. D.: Comparison of Changes in Mesenteric Resistance Following Splanchnic Nerve Stimulation with Responses to Epinephrine and Norepinephrine. Circulation Research **4:** 38 (Jan.), 1956.

Blood flow in the dog's superior mesenteric artery was measured with an electromagnetic flowmeter. In view of the fact that the resistance to blockade (to Ilidar) of the constrictor responses to splanchnic nerve stimulation corresponded more closely to intra-arterial injections of norepinephrine than to epinephrine, it would appear that the mediator of the neurogenically induced vasoconstriction is more likely norepinephrine. Since atropine was without effect on the apparent mesenteric dilator responses to nerve stimulation, the presence of cholinergic dilator fibers in the splanchnic nerves was not demonstrable.

AVIADO

Heisey, S. R., Saunders, J. P., and Olson, K. C.: Systemic Effects of 2-Isovaleryl-1,3-Indandione. Proc. Soc. Exper. Biol. & Med. **91:** 86 (Jan.), 1956.

The above anticoagulant produces a decline in blood pressure when given intravenously to cats in doses ranging from 5 to 60 mg./Kg. Concomitant with the decline in blood pressure there is an increase in respiratory rate and depth. The hypotension appears to be the result of rapid vasodilation

that has been described following dicumarol administration in dogs.

AVIADO

Malhotra, C. L., and Sidhre, R. K.: The Antiemetic Activity of Alkaloids of *Rauwolfia serpentina*. J. Pharmacol. & Exper. Therap. **116:** 123 (Jan.), 1956.

Reserpine and alseroxylon are markedly effective in antagonizing emesis in dogs induced by apomorphine, morphine, and ergot, but ineffective against emesis induced by veratrum and copper sulfate. Like chlorpromazine, the rauwolfia alkaloids appear to depress the chemoreceptor trigger zone in the medulla, which is the site of action of central emetics. Another point of similarity is depressant action on the hypothalamus of both drugs which is related to the hypotensive action of the rauwolfia alkaloids. It may be worthwhile to try these alkaloids as antiemetic agents in certain pathologic conditions, especially if they are associated with hypertension, as in toxemia of pregnancy.

AVIADO

Arora, R. B., and Madan, B. R.: Antiarrhythmics VI. Ajmaline and Serpentine in Experimental Cardiac Arrhythmias. J. Pharmacol. & Exper. Therap. **117:** 62 (May), 1956.

Ajmaline and serpentine, 2 alkaloids of *Rauwolfia serpentina*, have been found to be more active than quinidine in the following tests: (1) refractory period of isolated rabbit atria, (2) atrial fibrillation evoked in dogs by acetylcholine or aconitine, (3) atrial flutter produced in dogs by the injury-stimulation procedure, and (4) hydrocarbon-epinephrine-induced ventricular arrhythmias in dogs. Although projection of results from animal experiments to man is attended with hazards, it is suggested on the basis of these observations that ajmaline shows sufficient promise to warrant clinical trials in selected cases of cardiac arrhythmias.

AVIADO

Brody, T. M.: Action of Sodium Salicylate and Related Compounds on Tissue Metabolism in Vitro. J. Pharmacol. & Exper. Therap. **117:** 39 (May), 1956.

Sodium salicylate, aspirin, and methyl salicylate uncouple oxidative phosphorylation in liver, kidney, and brain mitochondrial preparations. The uncoupling action is qualitatively similar to that seen with the classical uncoupling agent, 2,4-dinitrophenol. The concentration of salicylates used in these studies is comparable to toxic levels in the intact animals. No attempt is made to relate these in vitro effects with the specific pharmacologic actions of the salicylates such as antipyresis, analgesia, or antirheumatic action. It is suggested that the toxic symptoms associated with salicylate overdosage could be attributed to the ability of this class of compounds to uncouple oxidative phosphorylation.

AVIADO

Cafruny, E. J., and Farah, H.: Effects of the Mercurial Diuretic, Mersalyl, on the Concentration of Protein-Bound Sulfhydryl, in the Cytoplasm of Dog Kidney Cells. J. Pharmacol. & Exper. Therap. **117:** 101 (May), 1956.

Renal protein-bound sulfhydryl concentrations were studied by a quantitative histochemical method. Mersalyl lowered the concentration of sulfhydryl cells of the terminal portions of proximal tubules, ascending limbs of the loops of Henle, and collecting ducts. BAL effectively counteracted mercurial diuresis and simultaneously restored sulfhydryl concentrations to control levels. These data parallel results previously obtained in rats and thus strengthen the view that the mechanism of mercurial action is somehow related to sulfhydryl systems, which in turn may actively support a renal transport mechanism. Protein-bound sulfhydryl could represent a large group of enzyme systems related to energy production or it may be a necessary component of the carrier substance postulated for the transport of electrolytes across membranes.

AVIADO

Agarwal, S. L., and Harvey, S. C.: Mechanism of Long Duration of Action of Dibenzyline. J. Pharmacol. & Exper. Therap. **117:** 106 (May), 1956.

After its local intra-arterial administration in the hind limb of dogs, dibenzyline can produce a local blockade without any evidence of a systemic blockade 24 hours after administration. Cross-circulation experiments reveal that the sojourn of an effective concentration of the drug in the donor cats circulation is no longer than 7 hours and was always incompletely transferred to the recipient cat. It is concluded that the long duration of action of this adrenergic blocking drug (peripheral vasodilator) is not due to its storage in body fat but is due to a firm chemical combination of the drug with a cellular receptor substance.

AVIADO

Curran, G. L., and Costello, R. L.: Reduction of Excess Cholesterol in the Rabbit Aorta by Inhibition of Endogenous Cholesterol Synthesis. J. Exper. Med. **103:** 49 (Jan.), 1956.

Hepatic cholesterol synthesis in rabbits, as measured by the incorporation of C^{14}-labeled acetate, was inhibited by addition of nontoxic amounts of vanadyl sulfate to the diet. This diet reduced excess aortic cholesterol in cholesterol-prefed rabbits when fed during a 6-week period. In both control and vanadium animals, following the cholesterol-prefeeding period, there is an almost complete mobilization of excess cholesterol from the various tissues except the aorta. During this period of time a

homeostatic effect is causing decreased hepatic cholesterol synthesis. When the concentration of hepatic cholesterol has been reduced toward normal in the control animals, there is a resumption of normal hepatic synthesis. Consequently, the degree of negative cholesterol balance is markedly lessened and mobilization of excess aortic cholesterol proceeds very slowly. In the vanadium-fed animals, however, this resumption of normal cholesterol synthesis is inhibited by the vanadium with maintenance of a negative cholesterol balance and resultant mobilization of more aortic cholesterol.

BERNSTEIN

Davies, B. M.: Disseminated Lupus Erythematosus, with Renal Involvement, Treated with Nitrogen Mustard. Brit. M. J. **1:** 670 (Mar. 24), 1956.

Dubois used nitrogen mustards in patients with lupus and renal impairment. The benefit seemed to be greatest in edematous patients. The 31-year-old female patient described by the author had a long-standing recurrent picture interpretable as lupus: polyserositis, generalized edema, blood urea nitrogen of 50 mg./100 ml., Krupp's telescopic urinary sediment, LE cells in the peripheral blood. Both cortisone and ACTH produced general clinical deterioration and severe mental disturbance without diuresis. The blood urea rose to 140 mg./100 ml. Within 2 days of nitrogen mustard therapy there was a marked diuresis. The patient became edema-free and the blood urea fell to 25 mg./100 ml. The patient was able to return to doing her own housework but there was still a trace of albuminuria, elevated erythrocyte sedimentation rate, and blood cholesterol of 550 mg./100 ml.

MCKUSICK

Moseley, V.: The Use of a Carbonic Anhydrase Inhibitor in the Treatment of Hyperkalemia. J. Am. Geriat. Soc. **4:** 58 (Jan.), 1956.

Seven case reports are given to indicate the therapeutic effectiveness of a carbonic anhydrase inhibitor (acetozoleamide) as an aid in the care of patients with chronic renal disease and patients with an increase in the level of serum potassium. The urinary excretion of potassium is increased. With repeated administrations of the drug, precautions must be taken to prevent an increase in metabolic acidosis.

RINZLER

Crouch, R. B., Hejtmancik, M. R., and Herrmann, G. R.: A Clinical Evaluation of Acetyl-Digitoxin. Am. Heart J. **51:** 609 (Apr.), 1956.

Acetyl-digitoxin by mouth was used in the therapy of 166 patients in congestive heart failure and was demonstrated to be a well-tolerated and effective new digitalis glycoside. Sixty-two of these patients were hospitalized and 104 were followed daily or every third day as ambulatory patients. The initial digitalizing dose can be given as a single dose or over a period of several days. The amount required must be adjusted for the patient, and usually varied from 1.6 to 2.0 mg., averaging 1.84 mg. In the single-dose method, 1.6 to 1.8 mg. was well tolerated, but occasionally supplementary amounts were necessary for full digitalization. Maintenance was also effective, and most patients could be maintained on 0.1 to 0.2 mg., the average being 0.15 mg./day. The excretion is slow, but appears somewhat more rapid than that of digitoxin. Toxic effects disappeared generally in 1 to 3 days, but the total elimination of drug effect from patients in atrial fibrillation required 13 to 17 days. Toxic effects were generally deliberately attained, and consisted of gastrointestinal symptoms in the majority of patients. There were no serious arrhythmias and no fatalities that could be ascribed to the drug. It appears that acetyl-digitoxin will attain merit as a long-acting glycoside that is well tolerated even in single digitalizing dosage by mouth and that is effective therapeutically. It has the advantage over digitoxin of somewhat more rapid dissipation, and toxic effects are usually gastrointestinal symptoms instead of potentially dangerous arrhythmias.

RINZLER

Satoskar, R. S., and Trivedi, J. C.: The Effect of Intravenous Digitalis on Cats under Hypothermia. Arch. pharmacodyn. **104:** 417 (Jan.), 1956.

It has previously been found that hypothermic rats treated with lanatoside C show less disturbances of rhythm during hypothermia. In dogs some beneficial effects of digoxin on right heart failure during hypothermia have been observed.

The authors studied 8 cats to determine the effect of digitalis glycosides during hypothermia. The animals were anesthetized with ether and pentobarbital sodium, 30 mg./Kg. In 4 animals serving as controls without hypothermia 12 ml. of Digilanid were infused. In the second group of 4 animals, cooling of the body with ice and water was employed. The temperature fell from 37–37.5 C. to 20–20.5 C. within 35 min. Digilanid was then given in the same amount as to the controls. The dosage required to produce cardiac arrest was found to be significantly higher during hypothermia.

The authors conclude that the observed changes in the RST segment and flattening of an inverted T wave during digitalis infusion signify a beneficial effect on the heart. An increase of the potassium content of the heart muscle following administration of therapeutic doses of digitalis is considered responsible.

SCHERF

Bellet, S., Wasserman, F., and Brody, J. I.: Further Observations on the Cardiovascular Effects of

Sodium Lactate: Effect in Normal Subjects and in Various Arrhythmias. Am. J. M. Sc. **231:** 274 (Mar.), 1956.

The effect of intravenous molar lactate was studied in 5 normal patients and in 27 patients with various conditions including partial A-V heart block, sinus bradycardia, carotid sinus sensitivity, and premature contractions. The effect of the infusion of 100 to 200 ml. of M sodium lactate upon the electrocardiogram, serum sodium, potassium, calcium, chloride, and blood pH was determined. Electrocardiographic changes were observed in patients with slow rates occurring with sinus bradycardia and A-V heart block. An increase in heart rate was observed in these patients with maximum changes being noted at or within a few minutes after completion of the infusion. Narrowing of widened QRS deflections was noted in 8 instances in this series. Carotid sinus sensitivity was unaltered in 4 subjects by lactate infusion. In 3 subjects, ventricular extrasystoles were observed during the course of infusion; these patients had advanced heart disease and 1 was noted to have digitalis toxicity. In 1 other patient without heart disease extrasystoles disappeared following lactate.

The possible mechanisms involved in the effect of sodium lactate upon the heart are not clear. A mild alkalosis manifested by an increase in pH and CO_2 combining power is noted regularly; electrolyte changes include a rise in serum sodium and a fall in potassium and calcium levels. The serum sodium increments are minor in degree and develop slowly. Whether the electrolyte shifts influence heart rate or whether the utilization of lactate itself by the myocardium is responsible for the observed cardiovascular effects cannot be stated at this time.

SHUMAN

Frick, P. G.: Hemorrhagic Diasthesis with Increased Capillary Fragility Caused by Salicylate Therapy. Am. J. M. Sc. **231:** 402 (Apr.), 1956.

Three patients were studied following the appearance of hemorrhagic symptoms while receiving salicylate therapy. Hematemesis, melena, and excessive bleeding from biopsy site were the manifestations observed. A battery of studies of the hemostatic mechanism was performed in each instance. All patients were found to have a positive Rumpel-Leeds test and abnormal bleeding time. No significant change in prothrombin time was noted. Interruption of salicylate therapy corrected the abnormal findings. Retreatment in 2 instances produced a recurrence of abnormal bleeding times and capillary fragility. The author concludes that salicylate represents an important factor to be considered in cases of acquired hemorrhagic diasthesis.

SHUMAN

Makous, N., Jennings, P., Funk, E. H., Jr., and VanderVeer, J. B.: A Clinical Evaluation of the Use of a Rectal Mercurial Diuretic in Patients with Chronic Congestive Heart Failure. Am. J. M. Sc. **231:** 86 (Jan.), 1956.

Mercaptomerin sodium (Thiomerin) was made available in suppository form in cocoa butter containing equivalent to 165 mg. of mercury in each dose. This preparation was administered to 23 patients under treatment for congestive heart failure receiving digitalis and previously given parenteral mercurial diuretics. In 5 instances, a double blind method was used. The effectiveness of suppository treatment was based on clinical findings and comparison of the number of weekly injections of mercurials before, during, and after its use. The mean parenteral mercurial requirement before suppository treatment was 1.2 injections/week. On an average of 7.3 suppositories/week, the mean number of injections decreased to 0.5/week. When suppositories were stopped, the injections increased to 1.2/week. The clinical response on suppository therapy was not significantly changed from that observed with mercurial injection therapy. The suppository treatment was not associated with local toxic or irritative effects despite prolonged use. It is concluded that mercaptomerin suppositories are effective in reducing or eliminating the need for parenteral mercury in the treatment of congestive heart failure.

SHUMAN

Hanley, T., and Platts, M. M.: Observations on the Metabolic Effects of the Carbonic Anhydrase Inhibitor Diamox: Mode and Rate of Recovery from the Drug's Action. J. Clin. Invest. **35:** 20 (Jan.), 1956.

Electrolyte studies were carried out in 2 normal adults. The observations indicate that recovery from the effects of the ingestion of the oral diuretic, Diamox, proceeds along mechanisms seen in other forms of metabolic acidosis. An exchange of Na^+ or K^+ for the secreted H^+ occurs; in this study 75 per cent of the increased H^+ excretion during recovery was associated with fixed cation conservation. It is also possible that chloride ion is withdrawn together with H^+, and is replaced by the bicarbonate ion.

The actual time needed for full recovery from the effects of this diuretic depends on the relative magnitudes of the original buffer depletion, and on the rate at which excess H^+ can be secreted by the renal tubules. The total buffer decrement caused by Diamox under the conditions of this study ranged from 250 to 400 mEq. There is evidence that 2 to 4 days are needed for electrolyte recovery from an initial single dose of the drug, and 5 to 6 days for full recovery from a series of doses.

WAIFE

PHYSICAL SIGNS

Kelly, J. Y.: Diagnostic Value of Phonocardiography in Mitral Stenosis. Mode of Production of First Heart Sound. Am. J. Med. **19:** 862 (Dec.), 1955.

The time of onset of the first heart sound is related to the simultaneous electrocardiogram in subjects with mitral stenosis, mitral insufficiency, and heart disease without mitral valve disease. A delay in the first heart sound occurred in patients with only mitral stenosis and proved of diagnostic value. The degree of delay paralleled the severity of the mitral stenosis. The mechanism by which the first sound is delayed in mitral stenosis can be readily explained by the hypothesis that the first heart sound is caused by sudden tensing of the atrioventricular valves and chordae tendineae when the atrioventricular septum is pushed in the direction of the atrium. In mitral stenosis, the left atrial pressure is high, while the end diastolic pressure in the left ventricle is low. The mitral valve does not close until the left ventricular pressure exceeds that of the left atrium. This disparity of pressures in the atrium and ventricle is found consistently in mitral stenosis. Significant shortening of the Q-first sound interval occurs with successful enlargement of the mitral orifice. Ventricular contraction does not contribute to the audible portion of the first sound. Moreover, this sound probably arises chiefly in the mitral rather than in the tricuspid valve. The length of the interval between the second sound and the opening snap of the mitral valve is generally inversely related to the severity of the mitral stenosis. This interval lengthens with successful mitral surgery. The presence of an opening snap is of great diagnostic significance. It is a more frequent finding in severe mitral stenosis than is a diastolic murmur.

Although the electric-mechanical intervals were determined by needle puncture of the ventricle at operation, this same information may be obtained by the simple, nonhazardous method of recording the apex impulse. The onset of the systolic deflection of the apex beat coincides perfectly with the ventricular pressure rise determined directly.

HARRIS

McKusick, V. A., Reagan, W. P., Santos, G. W., and Webb, G. N.: The Splitting of Heart Sounds. A Spectral Phonocardiographic Evaluation of Clinical Significance. Am. J. Med. **19:** 849 (Dec.) 1955.

Normal and pathologic conditions resulting in splitting of heart sounds are reviewed. The influence of respiration on splitting of the second sound can assist in identifying the type of bundle-branch block present and in distinguishing true splitting of heart sounds from simulating conditions. Arterial hypertension is not a cause of splitting of heart sounds. Asynchronism of valve closures is the fundamental basis for splitting of heart sounds and may have 2 general bases designated as electric (asynchronism resulting from ventricular activation abnormality as in bundle-branch block, ventricular extrasystoles, and idioventricular rhythm) and mechanical (asynchronism resulting from discrepancy in ventricular stroke volumes, as in atrial septal defect, or in rate of ejection, as in mitral and aortic regurgitation). In a patient over 40 years old, without other evidence of heart disease, striking inspiratory splitting of heart sounds suggests respiratory disease that is accompanied by exaggeration of intrapleural negativity of pressure during inspiration. Early and late systolic clicks and the mitral opening snap are the conditions most likely to simulate splitting of heart sounds.

Splitting of heart sounds is of limited diagnostic value in the pathologic states with which it may occur: interatrial septal defect, bundle-branch block, mitral or aortic regurgitation, and respiratory disease resulting in exaggerated cyclical variations in intrapleural pressure. In general, splitting has more significance (1) when it occurs in adults, (2) when splitting is exaggerated with expiration rather than with inspiration (left bundle-branch block), (3) when there is no clinical evidence of respiratory disease and labored respirations, and (4) when it persists throughout all phases of respiration (as is usually the case in interatrial septal defect).

HARRIS

Groom, D., Boone, J. A., and Jenkins, M.: Venous Hum in Cardiac Auscultation. J. A. M. A. **159:** 639 (Oct. 15), 1955.

The venous hum, a physiologic extracardiac murmur, heard in a high percentage of children and in some adults, is characteristically a continuous murmur with accentuation during diastole. The venous hum is louder with the subject in the sitting or erect position and diminishes or usually disappears altogether in recumbency. With the stethoscope on the point of maximum intensity over the jugular vein, light pressure tends to increase the intensity of the murmur and heavy pressure abolishes the sound. On auscultation over the precordium, pressure with the finger on 1 or both jugular veins will cause a murmur due to venous hum to disappear completely. Turning the subject's head away from the site of origin of the venous hum increases the murmur. It is more prominent during inspiration than during expiration. Its importance is that it may simulate pathologic murmurs.

KITCHELL

Miller, A. J., and Texidor, T. A.: "Precordial Catch." A Neglected Syndrome of Precordial Pain. J. A. M. A. **159:** 1364 (Dec. 3), 1955.

The common syndrome of precordial pain occurring in essentially healthy persons of light or medium body build in the younger age group (below 35 years) is described. The pain is severe, sudden in onset, does not radiate, and is regularly located near or above the cardiac apex. The pain occurs at rest or during mild activity and is frequently related to a "slouched" posture. This benign syndrome should

be considered in any differential diagnosis of precordial pain.

KITCHELL

Auinger, W.: Alterations of the Intensity of the First Heart Sound Under the Influence of Digitalis Glycosides in Absolute Arrhythmia. Ztschr. Kreislaufforsch. **44:** 889 (Nov.), 1955.

In 15 patients with atrial fibrillation and congestive heart failure variations of the intensity of the first heart sound were studied before and after intravenous injection of a digitalis preparation. Simultaneous piezoelectric registrations of the carotid pulse served for the determination of the time of isometric contraction and of the ejection time.

Moderate reduction of the ventricular rate by digitalis caused an increase; marked reduction, a decrease of the sound intensity. Under both circumstances the isometric contraction was shortened and ejection time lengthened. When this was related to the duration of the preceding diastole, a positive inotropic effect of digitalis could be demonstrated, regardless of the intensity of the first heart sound. This demonstrates that heart-sound intensity is primarily a function of the heart rate and may vary independently of cardiodynamic alterations.

PICK

Harris, T. N.: Phonocardiographic Study of Pulmonic-Systolic Murmurs in Children. Am. Heart J. **50:** 805 (Dec.), 1955.

Phonocardiographic tracings were taken of the presumably nonpathologic murmurs of children; those usually heard in the second intercostal space at the left sternal border. These tracings were compared with clearly identified murmurs of mitral valvular insufficiency and of some precordial vibratory (twanging-string) murmurs. The wave form of the pulmonary-systolic murmur showed some similarity to that of the precordial vibratory murmur, in that a simple wave could be discerned. However, whereas the form of the precordial vibratory murmur is generally quite uniform, resembling a sine wave of constant frequency, that of the pulmonic-systolic murmur almost invariably showed some distortion. Traces of pulmonic-systolic murmurs as obtained from patients with rheumatic fever, did not differ in any observable way as a group from those recorded from presumably normal subjects.

RINZLER

Ongley, P. A., Sprague, H. B. and Rappaport, N. B.: The Diastolic Murmur of Mitral Stenosis, New England J. Med. **253:** 1049 (Dec. 15), 1955.

It is pointed out that a murmur can be heard in presystole in cases of mitral stenosis with atrial fibrillation when diastole is short. No atrial systolic murmur is heard before the first sound of a ventricular premature beat but the presystolic murmur may also be absent in the beat that follows the ventricular premature beat. It is thought that this may be due to the fact that the left ventricle becomes so filled with blood during the long compensatory pause that atrial systole cannot force enough additional blood through the mitral orifice to produce a murmur. The Valsalva maneuver may convert a presystolic murmur into an atrial sound, producing a presystolic gallop, by decreasing venous return and in turn reducing the flow through the mitral valve orifice. The effects of mitral valve surgery upon the diastolic murmur have been found to vary greatly.

The opening snap of the mitral valve is described and the history of its appreciation is reviewed. It is due to a delay and accentuation of the normal fourth component of the second heart sound; that is, the opening of the atrioventricular valves. The opening snap must be differentiated from a third sound or a split second sound and, in conjunction with this latter question, it is mentioned that the opening snap, though usually heard best at the apex, may be heard best at the base. In relation to an apex cardiogram, the split second sound has its second component before the 0 point, an opening snap is synchronous with the 0 point, and a third sound occurs at the summit of the rapid inflow wave. So far as time intervals are concerned, the duration between the 2 components of a split second sound is usually less than 0.07 sec., the interval between the beginning of the second sound and the opening snap is at least 0.08 sec., and that between the beginning of the second sound and the third sound is about 0.12 sec. The opening snap may persist even when the murmurs of mitral stenosis become equivocal or absent as during atrial fibrillation, failure, or both.

The first heart sound at the apex is often loud and snapping in mitral stenosis. It is mentioned that earlier observers have noted that even when not increased in intensity the first sound may be delayed in displaying its main components. The authors point out that the third heart sound may be used as an index to the severity of mitral stenosis, since this sound is attributed to the rapid inflow of blood from the left atrium to the left ventricle early in diastole. This sound diminishes in intensity and finally disappears as the narrowed mitral orifice interferes with this rapid inflow.

The factors that reduce the intensity of the mitral diastolic murmur include a loud apical systolic murmur or loud opening snap or loud second heart sound, producing masking or fatigue effects upon the hearing mechanism of the examiner, tachycardia, congestive heart failure, or unusual features of distortion or deformity of the valve. In order to assist in the detection of the diastolic murmur the authors recommend auscultation under ideally quiet conditions, examination during moderate expiration, concentration on individual events of the cardiac cycle, using the bell of the stethoscope and adjusting the pressure with which it is held

against the chest very carefully, exercising the patient and turning him on his left side, searching the area of the apex carefully, and appreciating the many factors causing variations in the murmur.

ROSENBAUM

PHYSIOLOGY

Freedman, M. E., Snider, G. L., Brostoff, P., Kimelblot, S., and Katz, L. N.: Effects of Training on Response of Cardiac Output to Muscular Exercise in Athletes. J. Appl. Physiol. **8:** 37 (July), 1955. Abstracted, Circulation **14:** 199 (Aug.), 1956.

Sancetta, S. M.: Clinical Detection of "Pulsating" Liver. J. A. M. A. **158:** 922 (July), 1955. Abstracted, Circulation **14:** 253 (Aug.), 1956.

Dontas, A. S.: Effects of Energy Donors, Metabolic Inhibitors and Substrates on Carotid Chemoreceptor Activity. J. Pharmacol. & Exper. Therap. **115:** 46 (Sept.), 1955.

The chemoreceptors in the carotid body, which are known to be responsible for the circulatory and respiratory adjustments to anoxemia, were studied by intracarotid injection of agents related to carbohydrate metabolism. All high-energy phosphates tested (ATP, AMP, and pyrophosphate) excited the electric activity of the sinus nerve in the cat. Azide displayed excitatory action similar to and competitive to cyanide. Glucose and several other products of carbohydrate metabolism depressed chemoreceptor activity. Although the recordings were not derived from single fibers and were not correlated with reflex responses, they are suggestive evidence for new chemoreceptor excitants. The data show that several excitatory mechanisms may operate. Since uncoupling agents (which depress phosphorylation without affecting oxygen consumption) depressed or enhanced chemoreceptor activity, it is unlikely that the depression of oxidative phosphorylation is a factor influencing chemoreceptors.

AVIADO

Weidmann, S.: Effects of Calcium Ions and Local Anesthetics on Electrical Properties of Purkinje Fibers. J. Physiol. **129:** 568 (Sept.), 1955.

Calcium ions and local anesthetics are said to "stabilize" excitable membranes because in their presence, stronger currents are needed to stimulate the tissues, spontaneous rhythms are slowed, and conduction of impulses may be blocked. Single Purkinje fiber of calf's or sheep's heart soaked in calcium-rich solutions required more depolarization for excitation. Cocaine, procaine amide, quinidine, and diphenhydramine stopped spontaneous activity and blocked conduction of the fiber. The hypothesis is put forward that both calcium and local anesthetics act on the system that is responsible for carrying sodium ions through the surface membrane.

AVIADO

Beaconsfield, P., and Ginsburg, J.: The Effect of Body Posture on the Hand Blood Flow. J. Physiol. **130:** 467 (Nov.), 1955.

Alteration in posture from the supine to the erect normally involves a reduction in venous return (due to direct effect of gravity on the circulating blood) and reflex vasoconstriction to maintain blood pressure. The immediate response of the circulation in the hand to such a change in body posture is a vasoconstriction of short duration that is absent in the recently sympathectomized limb. This immediate vasoconstriction (seen in vertical position) is followed by a rise in blood flow to a mean level only slightly less than that recorded in the horizontal position. The sympathectomized hand in the late phase behaves similarly. It would appear that this response is not of nervous origin but may be a mechanical effect. One might therefore conclude that, in the long run, the vessels of the hand do not participate in the vasoconstriction that maintains blood pressure in the vertical position.

AVIADO

Mackay, I. F. S.: Rate of Drainage of the Blood Vessels of the Limbs by Gravity. J. Appl. Physiol. **8:** 169 (Sept.), 1955.

Simple plethysmographic technics are described for measuring the resistance to venous drainage from limbs of human subjects. Maximum drainage of the blood vessels by gravity occurs in approximately 30 to 35 sec. in the case of the legs, 15 sec. from the forearm and hand, and 5 sec. from the hand. An approximate assessment of the rate of venous drainage in the first 5 sec. gave the following results: Legs 26.0 ml., forearm and hand 53.3 ml., and hand 53.7 ml. The drainage rate is slower in the legs than in the arms, partly because the muscular action involved in raising the arm may have assisted in the venous drainage. It is apparent from these experiments that the normal limb is provided with a large reserve of drainage capacity to cope with increases of arterial inflow. The presence of edema when there is venous obstruction must be due to a fairly large increase of the obstruction to venous return.

AVIADO

Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himmelstein, A., Ravitch, M. M., and Gordon, A. J.: Timing of Electrical and Mechanical Events of the Left Side of the Human Heart. J. Appl. Physiol. **8:** 309 (Nov.), 1955.

Direct needle puncture of the cardiac chambers in 14 patients at operation revealed the following temporal relationships: interval from onset of P wave to onset of left atrial contraction averaged 0.068 sec.; interval from onset of Q wave in lead II to onset of left ventricular contraction averaged 0.041 sec.; isometric contraction period of left

ventricle averaged 0.050 sec. The reported latent periods for the left heart were shorter than those reported by others for the right heart when employing the catheter technic.

AVIADO

Price, H. L., and Helrich, M.: The Effect of Cyclopropane, Diethyl Ether, Nitrous Oxide, Thiopental, and Hydrogen Ion Concentration on the Myocardial Function of the Dog Heart-Lung Preparation. J. Pharmacol. & Exper. Therap. **115:** 206 (Oct.), 1955.

These anesthetic agents produced approximately equal depressant effects on myocardial contractility. However, the effects of thiopental appeared to be somewhat less than that of the other anesthetics. A decrease in blood pH of 0.5 unit also depressed myocardial contractility. If such effects apply to the human myocardium as well as to the dog heart-lung preparation, the cardiac effects of anesthetic agents per se may be augmented considerably during anesthesia as the result of respiratory acidosis.

AVIADO

Montini, T., and Paoletti, G.: Behavior of the Isolated Heart in Artificial Hypothermia. Arch. fisiologia **55:** 230 (Oct.), 1955.

Hearts of rabbits previously made hypothermic have been perfused with Ringer-Locke solution at 23 C. Coronary blood flow, mechanogram, and electrocardiogram have been compared with those of hearts isolated from normal animals, perfused initially with solution at 38 C. and gradually cooled to 23 C. In the first group of hearts the coronary flow was low, the mechanogram was normal, the electrocardiogram showed prolongation of Q-T, and essentially constant rhythm and contour. In the hearts cooled after isolation, the coronary flow gradually decreases, the rate becomes gradually slower, the mechanogram frequently shows an irregular sequence of systoles of varying amplitude, and arrhythmias, conduction defects, and variations in Q-T duration are also noted. Electrocardiographic changes occurring when the perfusion fluid is gradually rewarmed to 38 C. are also described.

CALABRESI

Beher, W. T., and Anthony, W. L.: Effects of β-Sitosterol and Ferric Chloride on Accumulation of Cholesterol in Mouse Liver. Proc. Soc. Exper. Biol. & Med. **90:** 223 (Oct.), 1955.

Since repeated experimental evidence has associated high cholesterol levels with atherosclerosis, various attempts have been made to lower blood and organ cholesterol content. The effects of several substances on cholesterol absorption have been studied using various experimental animals. Soybean sterols, consisting mainly of β-sitosterol, have been shown to decrease the accumulation of dietary cholesterol. Studies on dihydrocholesterol-treated animals have shown that this substance is also effective in reducing cholesterol absorption. Moreover, it has been found that, in the cockerel, precipitation of bile acids by ferric chloride results in a reduction of blood cholesterol. On the other hand, in the case of the mouse and rat, evidence has been produced that soybean sterols fail to lower organ and blood cholesterol.

The object of this investigation was to study first, the effectiveness of β-sitosterol in prevention of liver cholesterol accumulation and, second, the effectiveness of ferric chloride in a mammalian species.

Increasing the cholic acid content of a diet rich in cholesterol significantly increased total liver cholesterol. The addition of β-sitosterol to diets containing cholic acid and cholesterol decreased total liver cholesterol. Addition of ferric chloride, in varying amounts, to diets rich in cholesterol and cholic acid resulted in practically no change in total cholesterol content of mouse liver.

MAXWELL

Glendening, M. B., Cohen, A. M., and Page, E. W.: Influence of Pyridoxine on Transaminase Activity of Human Placenta, Maternal and Fetal Blood. Proc. Soc. Exper. Biol. & Med. **90:** 25 (Oct.), 1955.

There is some evidence that the altered tryptophane metabolism in normal pregnancy is the result of a deficiency in vitamin B_6, despite the fact that no evidence of B_6 deficiency has been demonstrated by blood, urine, or tissue levels of this vitamin. Pyridoxine derivatives, pyridoxal phosphate, and pyridoxamine phosphate probably serve as coenzymes of transamination reactions. Some tissues of pyridoxine-deficient animals have a reduced transaminase activity. Therefore, the authors investigated the effect of pyridoxine supplements on transaminase activity of certain fetal and maternal tissues as evidence of vitamin B_6 deficiency to justify large supplements of pyridoxine to diets of pregnant women.

The glutamic-aspartic transaminase activity of whole blood from normal pregnant subjects is essentially the same as in nonpregnant subjects. Activity is significantly increased by supplementing the diet with 10 mg. of pyridoxine daily. Transaminase activity of fetal blood is twice as great as in maternal blood in mothers not receiving additional vitamin B_6. The transaminase activity of placental tissue is not altered by prior administration of pyridoxine for several weeks. The results suggest that fetal tissues contain optimal quantities of B_6, whereas adults, both pregnant and nonpregnant, contain suboptimal concentrations for peak enzymatic activity. The method employed is not sufficiently sensitive to demonstrate a reduced "reserve" of B_6 in normal gestation, but the data are compatible with the view that pyridoxine supplementation is desirable in human pregnancy.

MAXWELL

Wróblewski, F., and LaDue, J. S.: Lactic Dehydrogenase Activity in Blood. Proc. Soc. Exper. Biol. & Med. **90:** 210 (Oct.), 1955.

The observation that during experimental and clinical myocardial infarction glutamic oxaloacetic transaminase is released from cardiac muscle resulting in increased enzyme activity in the serum suggested that other cardiac tissue enzymes behave similarly during myocardial infarction. Although present in other tissues in greater activity, lactic dehydrogenase, the enzyme concerned primarily with the reduction of pyruvic acid to lactic acid, is present in appreciable activity in cardiac musculature. In order to ascertain whether lactic dehydrogenase (LD) activity is increased in the serum during myocardial infarction, it was necessary to first demonstrate its presence in human and animal blood, and to delineate variations in LD activity in the blood of normal and diseased man.

LD activity is present in the venous serum of normal human adults. Normal activity ranges from 260 to 850 units/ml. with a mean value of 470 ± 130 units/ml. Venous whole blood hemolysates of normal adults have LD activity varying between 16,000 to 67,000 units/ml. with a mean value of 34,000 ± 12,000 units/ml. Alterations in serum LD have been studied in a selected group of disease states. Experimental and clinical myocardial infarction are associated with a rise in serum LD activity. LD, like serum glutamic oxaloacetic transaminase, rises in a characteristic fashion following myocardial infarction.

MAXWELL

Becker, E. L., and Joseph, B. J.: Measurement of Extracellular Fluid Volumes in Normal Dogs. Am. J. Physiol. **183:** 314 (Nov.), 1955.

Distributions of inulin and thiosulfate were simultaneously determined. Inulin distribution was 16–20 per cent and thiosulfate 20–25 per cent of body weight. The results were reproducible. Within 1 hour 53 per cent of thiosulfate was excreted in the urine. In 5 hours this quantity was 57 per cent as a maximum. Inulin was given by long constant infusion and the thiosulfate by a single intravenous injection that required 10 min. Since the metabolism of these 2 substances is different and the methods of administration varied, it is not surprising that they measured different volumes.

OPPENHEIMER

Rondell, P. A., Keitzer, W. F., and Bohr, D. F.: Distribution of Flow through Capillaries and Arteriovenous Anastomoses in the Rabbit Ear. Am. J. Physiol. **183:** 523 (Dec.), 1955.

With glass spheres of known size the arteriovenous anastomoses of the isolated rabbit's ear were found to be 47–59 μ. There were only a limited number of vessels between this size and that of capillaries. A group of experiments were carried out with spheres of 30 μ in diameter. These would pass through anastomoses but not capillaries. By this method the mean shunt flow was 36.0 per cent of the total flow. There was a spontaneous variability in this flow of almost ±10 per cent. This shunt flow was largely independent of perfusion pressure in the range 45–105 mm. Hg.

OPPENHEIMER

Maurea, G., Nylin, G., and Sollberger, A.: Normal Heart Volume. Acta. cardiol. 10: 336 (Fasc. 4), 1955.

A statistical evaluation is presented of data on normal heart volume assembled in 763 healthy subjects between 9 and 66 years of age. The heart volume was determined roentgenologically by a method developed by the author and his associates, and correlated with height, body weight, body surface, the basal metabolism, and O_2 consumption after work. Means and standard deviations of the factors studied are tabulated, and correlation coefficients, regression lines, and standard deviations around the latter are indicated in diagrams.

The correlations, heart volume/body weight and heart volume/body surface, are almost equal (0.41 and 0.44 for men, 0.58 and 0.53, respectively, for women) and agree with the results of previous reports. The possible errors, differing in the 2 sexes are discussed. They attain 2 to 13 per cent when cardiac volume is correlated with square meters of body surface, 20 to 33 per cent when correlated with body weight in kilograms, and sometimes reach 100 per cent in correlations with age. Hence, in spite of the equality of correlations with body surface and body weight, the former is to be preferred when relative heart volumes are calculated.

The results of this study are applicable only for comparison of normal values with normal standards. Other correlations and errors can be expected in pathologic cases.

PICK

Michel, D., Herbst, M., Hartleb, O., and Bock, K.: The Diagnostic Validity of the "Oxygen Jump" During Cardiac Catheterization. Ztschr. Kreislaufforsch. **44:** 902 (Nov.), 1955.

The authors applied statistical methods to define criteria for a left-to-right shunt in terms of O_2 differences found photometrically in blood samples obtained by cardiac catheterization.

An atrial septal defect or anomalous return of pulmonary veins can be assumed to be present when the O_2 concentration of the right atrial blood exceeds by 2.5 vol. per cent that of 1 of the venae cavae, preferably the one with the higher O_2 content. An O_2 difference of 1.7 vol. per cent between the right ventricle and atrium, or between right ventricular and pulmonary artery is sufficient to diagnose a ventricular septal defect or a patent ductus respectively. These requirements of O_2 differences can be

reduced by ⅓ when average values of 3 to 5 samples obtained in different adjacent portions in a heart chamber or in the pulmonary artery are obtainable. Multiple samples from the same position but with varying O_2 contents can be used for a shunt diagnosis when the difference between 2 such samples is more than 1.3 vol. per cent in the right atrium, 1.2 vol. per cent in the right ventricle and 0.9 vol. per cent in the pulmonary artery. The O_2 content in the 2 venae cavae can show considerable differences and can imitate a left-to-right shunt in the atria. In order to avoid diagnostic errors, samples of blood from both these vessels should be obtained and included in the gasometric analysis.

PICK

Sobel, H., Myers, S. M., and Marmorston, J.: A Procedure for the Quantitative Determination of Protein of the Rat Heart. Circulation Research **3:** 454 (Sept.), 1955.

Several procedures for the fractionation of the proteins of a single rat heart are described and a reproducible method for the quantitative determination of the extractable proteins is presented. A sucrose-versene solution was used for primary extraction. Following centrifugation and further extraction with a phosphate-pyrophosphate buffer, low ionic-strength-extractives, a mitochondrial fraction, and high-ionic-strength extractives were obtained. Electrophoretic analysis of these extracts demonstrated the presence of 5 proteins in the low-ionic-strength extracts and 3 subfractions in the high-ionic-strength extracts.

SAGALL

Hendricks, C. H., and Quilligan, E. J.: Cardiac Output in Pregnancy: Correlation between Evans Blue Dye and Blood Pressure Methods. Circulation Research **3:** 506 (Sept.), 1955.

A total of 30 cardiac output determinations were performed in 23 young healthy patients in late pregnancy, during labor, or in the early puerperium. The cardiac output as estimated by means of the pulse pressure method was compared to that determined by the Evans-blue-dye method. In 21 tests the cardiac output was determined by both methods simultaneously. Of the 30 determinations, 27 (90 per cent) of the cardiac output determinations as measured by the blood pressure method agreed with the dye-measured outputs within 25 per cent.

SAGALL

Albrink, M. J., Hald, P. M., Man, E. B., and Peters, J. P.: The Displacement of Serum Water by the Lipids of Hyperlipemic Serum. A New Method for the Rapid Determination of Serum Water J. Clin. Invest. **34:** 1483 (Oct.), 1955.

In lactescent serums the insoluble lipids may displace serum water sufficiently to produce errors in determinations of water-soluble substances. Misleadingly low concentrations of electrolytes may be found. However, when the insoluble lipids are removed by ultracentrifugation, the electrolytes in the clean fluid may be entirely normal.

The authors describe a method for the rapid determination of serum water based on freezing point depression after the addition of salt. This method checks rather well with the gravimetric technic. By studying water displacement by serum proteins the authors found that a rough estimate of the water (in Gm./100 ml. serum) displaced by serum lipids is about 0.04 times the total fatty acids in mEq./L.

WAIFE

Lee, G. de J., and DuBois, A. B.: Pulmonary Capillary Blood Flow in Man. J. Clin. Invest. **34:** 1380 (Sept.), 1955.

This paper describes a method for measuring instantaneous blood flow in the pulmonary capillary system in man. Using an airtight body plethysmograph, a continuous recording of pressure is made before and after nitrous oxide inhalation. As the gas is absorbed by blood entering the pulmonary capillaries, the pressure within the body plethysmograph falls. The rate of gas uptake is proportional to capillary flow. The flow in normal subjects was found to be pulsatile with a rapid acceleration of flow to a rate about twice the mean cardiac output followed by a gradual decline. This cycle is repeated with each ventricular contraction.

It may be difficult to assume a single value for pulmonary capillary blood volume on the basis of a constant flow as had sometimes been assumed. The pulsatile flow may produce certain hemodynamic and gas exchange effects not fully appreciated. Thus the ratio of mean pressure to mean flow commonly known as "pulmonary arteriolar resistance" will include components of elasticity and inertia. The authors suggest the temporary use of the term "pulmonary impedance."

WAIFE

McDowall, R. J. S., Munro, A. F., and Zayat, A. F.: Sodium and Cardiac Muscle. J. Physiol. **130:** 615 (Dec.), 1955.

The contractions of a strip of isolated rat heart muscle in Kreb's solution are markedly affected by the sodium content of its environment, being depressed by increased sodium content and augmented by reduction. Since the depression caused by anoxia can be relieved by reducing the sodium in the bath, it is suggested that anoxia brings about an increase in the sodium uptake by the muscle. Thus cardiac muscle is brought into line with the well-known fact that in conditions of salt loss (i.e., intense diarrhea and sweating) stripped muscle is liable to go into states of excessive contraction.

AVIADO

Pletscher, A., Shore, P. A., and Brodie, B. B.: Serotonin as a Mediator of Reserpine Action in Brain. J. Pharmacol. & Exper. Therap. **116:** 84 (Jan.), 1956.

The administration of reserpine to rabbits in doses as low as 0.1 mg/Kg. releases serotonin in the brain. The normal occurrence in brain of both serotonin and the potent enzyme, amine oxidase, makes it appear probable that serotonin exists mainly in a bound form. The significance of these results in terms of therapy of hypertension remains obscure.

AVIADO

Holton, P.: Antidromic Vasodilatation in the Isolated Perfused Ear of the Rabbit. J. Physiol. **131:** 176 (Jan.), 1956.

It is common experience that vasodilatation is more difficult to obtain in organs perfused with salt solution than in the intact animal. Perfusion of the ear vessels with heparinized horse blood or washed red corpuscles in a dextran solution kept the vessels sensitive to antidromic vasodilatation. That antidromic vasodilatation could be obtained repeatedly, even in the absence of plasma, suggests that such affects may not be due to the local production of vasodilator substance from plasma proteins. It is possible, however, that proteins derived from interstitial fluid or from slight progressive hemolysis occurring during the experiment may have participated in the vasodilator responses.

AVIADO

Haddy, F. J., and Gilbert, R. P.: The Relation of a Venous-Arteriolar Reflex to Transmural Pressure and Resistance in Small and Large Systemic Vessels. Circulation Research **4:** 25 (Jan.), 1956.

The role of transmural pressure (absolute level of intraluminal over extraluminal pressure) in determining vascular resistance in the forelimb of a dog was investigated by measuring pressures in the brachial vessels in the small (1-mm. diameter) vessels. Elevation of pressure in the veins, small vessels and arteries by venous obstruction with flow rate constant was associated with no change in total resistance but elevated small vessel resistance. When all the nerves were blocked high in the leg with procaine, total resistance decreased and the small vessels failed to constrict. A "venous-arteriolar reflex" is postulated on the basis that elevation of arterial pressure alone did not elicit small vessel constriction. It is not absolutely certain if the sympathetic or somatic nerves are involved at all, since the local anesthetic may be carried distally to affect the local reactivity of the vessels. Surgical denervation will help establish this reflex, which may in turn explain the increased vascular resistance of congestive heart failure.

AVIADO

Garb, S. and Penna, M.: Some Quantitative Aspects of the Relation of Rhythm to the Contractile Force of Mammalian Ventricular Muscle. Am. J. Physiol. **182:** 601 (Sept.), 1955.

Interpolated extra beats augment the next beat but this augmentation decreases regularly in those that follow. Augmentation of the first beat after the interpolated extra beat is increased when this extrasystole occurs closer to the last regular beat. Rest after the extra beat allows the augmentation to reach a peak in 10 sec. and persist for 5 min. It is pointed out that the augmentation cannot depend on decreased time interval for diffusion of substances into or out of the cell because of this previously mentioned finding. During diastolic pauses, the heart muscle is probably not at rest, but is building up energy for the next contraction.

OPPENHEIMER

Denolin, H., Hanson, J., and Leulme, J.: Hemodynamic Study of Interatrial Communications. Acta. cardiol. **11:** 12 (Fasc. 1), 1956.

The authors reviewed clinical, hemodynamic and electrocardiographic data collected in 27 cases with proved interatrial communication and arrived at the following conclusions. As a rule this congenital malformation produces, through an arteriovenous shunt, a marked increase in pulmonary flow, without significant elevation of pulmonary arterial pressure. These findings account for the clinical and radiologic aspects of the disease including the hypertrophy of the right ventricle, the enlargement of the pulmonary artery and its branches, and the marked pulsation of these vessels. With increasing age, usually after 40 years, the pulmonary arterial pressure begins to rise and this may lead to the development of right heart failure. Such a slow course of evolution of the disease justifies surgery in younger persons. In exceptional instances, an atrial septal defect may be associated with pulmonary hypertension in infancy and then the interatrial shunt is partially or completely reversed. Under such circumstances the walls of the pulmonary vessels may show significant anatomic alterations and even calcification. Such a condition is badly tolerated and not amenable to surgery. The outstanding electrocardiographic feature is a right-sided ventricular conduction defect, the degree of which depends on the extent of the hemodynamic alterations.

PICK

Rodbard, S.: Distribution of Flow through a Pulmonary Manifold. Am. Heart J. **51:** 106 (Jan.), 1956.

A specially designed manifold of glass and rubber tubes was perfused with water to simulate certain mechanical aspects of the pulmonary circulation. A pressure head (pulmonary artery) caused flow through 4 tubes in parallel (pulmonary arterioles) spaced 10 cm. apart. Vertical positioning of such a pulmonary manifold caused preferential flow through the dependent channels, while little perfused the

elevated portions. This effect was exaggerated at low pressure heads. As the pulmonary arterial pressure head was raised, the elevated or apical segments received an improved supply. Slight to moderate "intrapulmonary" air pressure, uniformly applied to all 4 "capillaries," shunted flow away from the elevated vessels and increased that through the dependent tubes. High levels of such air pressure reduced flow as a whole and resulted in a requirement of a high pulmonary arterial pressure if "normal" flow was to be perfused through the "lung." Elevation of the level of the outlet (pulmonary venous pressure) increased flow through the elevated segments until it equaled that through the base. When the (intrapulmonary) air pressure was then raised, the apical flow was markedly reduced and almost the entire flow shunted through the dependent channels. Enhancement of precapillary resistance equalized flow through the elevated and dependent portions of the manifold, but reduced the total flow for a given pressure head, thereby requiring a higher arterial pressure to maintain perfusion of the system at "normal" flow rates. Elevation of intrapulmonary air pressure in these circumstances had only a limited effect in redistributing flow to the base. Alterations in blood flow have clinical implications in such conditions as pulmonary hypertension subsequent to arteriosclerosis of the lesser circulation, emphysematoid states, congestive heart failure, orthopnea, the tendency to pulmonary edema in the dependent portions of the lung, and the predisposition to apical involvement of reinfection tuberculosis.

RINZLER

Singer, R. B., Deering, R. C., and Clark, J. K.: The Acute Effects in Man of a Rapid Intravenous Infusion of Hypertonic Sodium Bicarbonate Solution. II. Changes in Respiration and Output of Carbon Dioxide. J. Clin. Invest. **35:** 245 (Feb.), 1956.

Respiratory and acid-base changes during and following sodium bicarbonate infusion were studied in healthy subjects. During the infusion there was an increase in total ventilation, indicating respiratory stimulation (and increased CO_2 output). Unlike other alkalinizing solutions, sodium bicarbonate produced a biphasic response, i.e., a decrease in ventilation *after* the infusion. The authors discuss the physiologic mechanism involved in this form of experimental metabolic alkalosis.

WAIFE

Schwartz, I. L., and Thaysen, J. H.: Excretion of Sodium and Potassium in Human Sweat. J. Clin. Invest. **35:** 114 (Jan.), 1956.

Previous studies on sweat metabolism have usually dealt with the whole-body response. In this work localized sweating was produced by the intradermal injection into the forearm, of Mecholyl, a cholinergic drug. Sweat was collected by standard procedures.

The findings support the concept that both sodium and potassium are delivered into a precursor solution, and sodium, but not potassium, is reabsorbed by a subsequent process of limited capacity.

WAIFE

Bronner, F., Harris, R. S., Maletskos, J., and Benda, C. E.: Studies in Calcium Metabolism: The Fate of Intravenously Injected Radiocalcium in Human Beings. J. Clin. Invest. **35:** 78 (Jan.), 1956.

Calcium metabolism is incompletely understood in man. In this study radiocalcium (Ca^{45}) was administered intravenously to 9 adolescent boys and 1 young man, all of whom were normal except for mental inadequacy.

The urine contained from 1½ to 2 times the quantity of radiocalcium excreted in the feces. Calculations reveal that about 15 per cent of the average daily fecal output of calcium in the adult was endogenous in origin. Only a minor fraction of the calcium absorbed on any 1 day is re-excreted promptly; the major portion is retained for some time. The peak output of Ca^{45} in the feces occurred on the second or third day. Excretion was low, for in no case did the combined output of isotope exceed 7 per cent of the injected radiocalcium during any 1 day. Nearly all the calcium that enters the body at a given moment is at first retained, presumably chiefly by the skeleton, and equilibrium is maintained by excreting calcium that had been previously absorbed.

WAIFE

RHEUMATIC FEVER

Barnum, D. R.: Gross Pulmonary Hemorrhage Due to Mitral Stenosis. Quart. Bull. Northwestern Univ. M. School. **29:** 205, 1955.

A case is reported of a 30-year-old white man who claimed good health and denied rheumatic fever, heart disease, or any symptoms thereof prior to the onset of profuse hemoptysis. He developed pulmonary edema and had a massive pulmonary hemorrhage due to what proved to be rheumatic mitral stenosis. The occurrence of hemoptysis in mitral stenosis is briefly discussed in the light of other authors' findings and of experience at a general hospital.

BERNSTEIN

Klein, R., and Harris, S. B.: Treatment of Scleroderma, Sclerodactylia and Calcinosis by Chelation (EDTA). Am. J. Med. **19:** 798 (Nov.), 1955.

A chelating agent, ethylenediamine tetracetic acid (EDTA), was used in the treatment of a patient with typical scleroderma, sclerodactylia, calcinosis, and arthritis (rheumatoid?). Treatment was fol-

lowed by improvement as indicated by x-ray evidence of marked diminution in the articular and cutaneous metastatic calcific deposits, histologic evidence of regression of the sclerodermatous changes in the skin, and return of mobility of the affected joints. The chelating agent was probably responsible for the remission. During treatment there was a definite increase in the output of urinary calcium, but no marked change in the level of serum calcium.

HARRIS

Batterman, R. C., and Grossman, A. Z.: Effectiveness of Salicylamide as an Analgesic and Antirheumatic Agent. J. A. M. A. **159:** 1619 (Dec. 24), 1955.

In view of the interest shown in salicylamide for its analgesic and antirheumatic effect, it was thought advisable to study both of these under conditions that would lead to statistical evaluation with placebo and other salicylate therapy. It was found that salicylamide is not an effective analgesic or antirheumatic medicament in man. The double-blind technic showed no differentiation between placebo or effective medicaments when applied to an evaluation of analgesic and antirheumatic drugs in ambulatory patients. Each investigative group should determine the responsiveness to placebo medication for its particular type of patients and use these data as a control for evaluation of unknown analgesic or antirheumatic drugs.

KITCHELL

Matthews, M. B., Medd, W. E., and Gorlin, R.: Aortic Stenosis: A Clinical Study. Brit. M. J. **2:** 759 (Sept. 24), 1955.

The authors observed aortic stenosis in a predominantly male group of 50 patients, especially in the "undetermined" group without evidence of congenital or rheumatic basis. In fact, in the latter 2 groups females predominated. There were 6 cases classified congenital and, in addition, the drawing is shown of the specimen in a 6-year-old boy with aortic stenosis "due to fibro-elastosis." In 20 cases rheumatism was considered the certain basis of the valve deformity. In the remaining 2 cases the cause was "undetermined."

In general, the clinical findings of the authors are in agreement with those presented by other students of this subject. In 30 of the 50 patients, the second aortic sound was normal. The aortic systolic murmur tended to diminish during cardiac failure. Prominence of the first part of the aorta to the right and anteriorly was observed in 30 of the 50 patients.

The critical value area in isolated aortic stenosis seemed to be 0.5 cm.^{2} but was larger if there was co-existing regurgitation.

The familiar natural history of aortic stenosis—rapid deterioration after symptoms once have their onset, sudden death at any time including the asymptomatic period—is reviewed.

One case, presumably congenital, had calcification of the aortic valve.

MCKUSICK

Gil, J. R., Rodriguez, H., and Ibarra, J. J.: Incidence of Asymptomatic, Active Rheumatic Cardiac Lesions in Patients Submitted to Mitral Commissurotomy and the Effect of Cortisone on These Lesions. Clinical and Histopathologic Study of Sixty Cases. Am. Heart J. **50:** 912 (Dec.), 1955.

Sixty patients submitted to mitral commissurotomy were studied. Fourteen of them were treated with cortisone before as well as after surgery in order to evaluate the incidence of asymptomatic but active cardiac rheumatic lesions, the effects of cortisone on these lesions as well as upon the inflammatory reactions secondary to the surgical trauma, and whether or not the postoperative follow-up in the treated patients is more favorable than in the untreated group. A large group (60 per cent) of patients submitted to commissurotomy shows active but asymptomatic rheumatic cardiac lesions. The use of cortisone diminishes the presence of such lesions from 67.4 per cent to 35.7 per cent. It increases the frequency of lesions moving toward cicatrization or already healed from 10.9 per cent to 28.6 per cent and from 21.7 per cent to 35.7 per cent, respectively. Cortisone can decrease the inflammatory surgical reactions of the pericardium and endomyocardium. Through clinical, phonocardiographic, electrocardiographic, and histopathologic studies the frequency of pericarditis has been shown to decrease from 86.3 per cent to 38.4 per cent, from 72.7 per cent to 36.3 per cent, and from 50 per cent to 21.4 per cent, respectively. It was not possible to establish clearly a better evolution in the postoperative period in those patients treated with cortisone as compared with the untreated. However, relapses and postcommissurotomy syndrome were less frequently observed in the first group.

RINZLER

Perlstein, I. B.: Histamine as a Stress-Combating Agent in the Treatment of Rheumatic Disease. J. Am. Geriatrics Soc. **3:** 997 (Dec.), 1955.

Sixty-five patients, manifesting various features of rheumatic disease (bursitis, fibrositis, arthritis), were treated with injections of aqueous histamine diphosphate. In the last 10 patients (chronologically) repository histamine (Histapon) was employed to supplement the action of the aqueous preparation. The repository preparation kept these patients symptom-free for longer periods of time, obviated the necessity for frequent injections of aqueous histamine, and permitted lengthening of the interval between injections. Most of the patients had experi-

enced painful rheumatic disorders for long periods of time and had received the usual treatment (x-ray, gold, salicylates, phenylbutazone, cortisone, and ACTH). These previous treatments had been failures. Such patients required longer treatment with histamine. Other patients in this series with rheumatic disorders of more recent origin made more dramatic recoveries and required treatment for shorter periods of time. The marked improvement bears a striking resemblance, in terms of symptom-response, to that which may be achieved with cortisone or ACTH, with this important difference: side effects which are common during administration of these hormones do not occur with the histamine preparations. Similarly, eosinopenia resulting from histamine treatment resembles that achieved with cortisone or ACTH. This profound decrease in circulating eosinophils occurs much more rapidly and more definitely with histamine. The improvement in the course of the disease and the satisfactory response to histamine are closely paralleled by the fall in eosinophil levels. There were 4 therapeutic failures in this series of 65 patients, all of them in patients with atrophic arthritis. In all 4 there was no effect on the eosinophil count.

RINZLER

Gluck, E. J., Brandt, A. A., and Dordick, J. R.: Prednisone in Active Rheumatic Carditis. New England J. Med. **253:** 518 (Sept. 22), 1955.

A case of a 55-year-old woman with rheumatic heart disease and congestive heart failure is presented in detail. A diagnosis of progressive acute rheumatic carditis was made because of a protracted febrile course, changing auscultatory phenomena, increasing cardiac enlargement, recurrent arthralgias, persistent prolongation of the P-R interval, and compatible changes in the laboratory tests. The patient received 7210 mg. of cortisone in 39 days, 2525 mg. of prednisone over 47 days, and 265 mg. of prednisolone over 6 days. No clinical amelioration of the rheumatic carditis resulted. An intercurrent pulmonary infection occurred while the patient was receiving prednisolone, with precipitation of acute left ventricular failure and death. Although there were calcific changes in both the mitral and aortic valves, the myocardium showed abnormalities suggesting rheumatic myocarditis. An acute gastric ulcer was also found to be present. While receiving prednisone and a diet containing 5 Gm. of sodium, substantial retention of sodium occurred. Histologic examination of the adrenal glands also disclosed atrophy of the inner 2 layers although it was less in degree than that reported in patients receiving the usual doses of cortisone.

ROSENBAUM

Aitchison, J. D., Cranston, W. I., and Priest, E. A.: The Effects of l-Hydrazinophthalazine on the Pulmonary Circulation in Mitral Disease. Brit. Heart J. **17:** 425, 1955.

Ten to 20 mg. of l-hydrazinophthalazine introduced into the pulmonary artery of 10 individuals with mitral valve disease produced in 9 a rise in pulmonary artery pressure, tachycardia, and a slight increase in cardiac output. The higher the mitral pulmonary artery pressure, the higher was the rise. The rise tended to outlast the tachycardia.

The use of l-hydrazinophthalazine appears contraindicated in individuals with hypertension associated with mitral valve disease.

SOLOFF

Davis, E., and Landau, J.: Capillary Microscopy in Rheumatic Fever. Arch. Int. Med. **97:** 51 (Jan.), 1956.

The capillaries of the conjunctiva and the nailbed have been studied by both slit-lamp and capillary microscopy in 100 patients with acute rheumatic fever or rheumatic heart disease. A characteristic capillary pattern was found in the conjunctiva of 79 patients and in the nailbed in 31 of these 100 patients—a considerably higher proportion than was found among control patients. In the conjunctiva, the special feature is the repeated subdivision of vessels (arborization) and the abrupt thinning of many of the terminal vessels, which often appeared to terminate as end-vessels, having no apparent connection with adjacent vessels. This was in marked contrast with the usual picture of an interlacing latticework of the small conjunctival vessels. In the nailbed, the capillaries often branched from a common stem, giving the appearance of multibranched candlesticks. The possibility that the pattern may be present before the onset of rheumatism and may be a sign of a rheumatic diathesis is discussed. The presence of these capillary signs may help diagnosis in borderline cases.

BERNSTEIN

Glaser, R. J., Thomas, W. A., Morse, S. I., and Darnell, J. E.: The Incidence and Pathogenesis of Myocarditis in Rabbits after Group A Streptococcal Pharyngeal Infections. J. Exper. Med. **103:** 173 (Jan.), 1956.

Rabbits subjected to pharyngeal infections with group A streptococci developed cardiac lesions characterized by myofibril necrosis and a nongranulocytic cellular reaction. The histopathologic changes were demonstrable within 24 hours of inoculation, were maximal 72 hours after induction of infection and, thereafter, healed in the course of the following 2 weeks. The extent of involvement was variable, and with healing the necrotic areas were replaced by fibrous tissue.

When intradermal infections with the same organisms were produced in rabbits, cardiac lesions, indistinguishable from those observed in the pharyngeally infected group, appeared in a much smaller number of animals.

The hearts of 5 of 6 rabbits sacrificed a month or

more following the last of a series of streptococcal pharyngeal infections, exhibited lesions characterized chiefly by fibrosis, although mononuclear cellular infiltrations were also noted. In these repetitively infected animals, the presence of occasional multinucleated giant cells and a few small foci of calcification were features not encountered in the single infection group. In none of the lesions were bacteria demonstrable, either in histologic sections or in cultures of myocardial tissue. The implications of these findings, in terms of the nonsuppurative sequelae of streptococcal infections in man, are discussed.

BERNSTEIN

Tedeschi, C. G., and Wagner, B. M.: The Problem of Subclinical Rheumatic Carditis. Am. J. M. Sc. **231:** 382 (Apr.), 1956.

Using certain criteria for the detection of an active rheumatic process in tissues, the authors examined 400 auricular appendages obtained from patients undergoing cardiac surgery for the treatment of valvular disease. The findings of Aschoff body of juvenile character, alteration in collagen fibers and ground substance, exudative inflammatory reaction in the section, and degeneration of myofibers were regarded as indicating the presence of an active rheumatic carditis. Eight of the tissues submitted presented an appearance of active carditis. In 67 additional cases, Aschoff bodies of the senescent type were described together with myocardial and endocardial fibrosis, findings consistent with a diagnosis of healed rheumatic carditis. In the remaining 324 appendages no Aschoff bodies were found. In this series 22 patients died shortly after mitral commissurotomy; the findings in other areas of heart muscle were similar to those seen in the auricular appendage. Extensive preoperative studies revealed no sign of rheumatic activity except for the sedimentation rate which, in the majority, correlated with pathologic findings. The postoperative course was similar in all groups of cases, with no signs of recrudescence of rheumatic activity.

SHUMAN

Lustok, M. J., and Kuzma, J. F.: Rheumatic Fever Pneumonitis: A Clinical and Pathologic Study of 35 Cases. Ann. Int. Med. **44:** 337 (Feb.), 1956.

The clinical diagnosis of rheumatic fever pneumonitis is warranted when there is (1) disproportionate respiratory distress with severe cough, chest pain, cyanosis, and hemoptysis, not relieved by oxygen and the customary supportive measures, (2) evidence of carditis, but not of sufficient severity to explain the pulmonary findings, in the presence of prolonged high fever and negative blood cultures that do not respond to salicylates, (3) chest x-ray finding of increased perivascular markings arising at the hilus and progressing to nodulation, confluence, and massive consolidation with relatively clear apices and bases. The gross pathologic changes are rubbery consistency, various dark hues of focal hemorrhages, fine granularity, and spotty vesicular emphysema. The histologic changes are alveolar hemorrhages, necrotizing alveolitis, hyaline membranes, alveolar lining-cell proliferation, organization of exudate, fibrinoid necrosis of the bronchiolar lamina propria, and arteritis.

WENDKOS

ROENTGENOLOGY

Singleton, E. B., McNamara, D. G., and Cooley, D. A.: Retrograde Aortography in the Diagnosis of Congenital Heart Disease In Infants. J. Pediat. **47:** 720 (Dec.), 1955.

The diagnosis of congenital cardiac abnormalities in infants by usual clinical, fluoroscopic, and radiologic technics is difficult because as the authors point out, physical signs are unreliable, characteristic radiographic patterns are not present, since not enough time has elapsed for their development, and usually an enlarged thymus shadow obscures cardiac boundaries. The authors have made use of an additional technic: retrograde aortography by the introduction of a radiopaque medium into the brachial artery and thence into the aorta. They present the clinical history and x-ray findings using this technic of 5 cases whose doubtful diagnosis was established. These cases were ones of patent ductus, coarctation of the aorta, truncus arteriosus, ventricular septal defect, and aortic stenosis.

HARVEY

Torrance, D. J.: Demonstration of Subepicardial Fat as an Aid in the Diagnosis of Pericardial Effusion or Thickening. Am. J. Roentgenol. **74:** 850, 1955.

The author describes preliminary results where subepicardial fat layers were demonstrated that had a lesser density than the overlying pericardial fluid or thickening. Rapid laminography (1/60 to 1/20 sec.) is preferable to show this difference, but on several occasions the perivascular fat deposits were demonstrable with the aid of the usual current types of laminographic technics.

SCHWEDEL

Fleischner, F. G., and Sagall, E. L.: Pulmonary Arterial Oligemia in Mitral Stenosis as Revealed on the Plain Roentgenogram. Radiology **65:** 857 (Dec.), 1955.

The authors present the progressive changes occurring in the hilar shadows of patients followed for 4 to 15 years. Along with progressive widening of the pulmonary arteries they stress the narrowing of the tertiary and smaller branches and correlate such findings with the deterioration in the clinical state from group I (New York Heart Association criteria) to groups III and IV.

Evidence is cited in favor of a relationship between such narrowing (with resulting oligemia of the lung) and increased pulmonary arterial pressure and resistance.

SCHWEDEL

Tillander, H.: Selective Angiography of the Abdominal Aorta with a Guided Catheter. Acta radiol. **45:** 21 (Jan.), 1956.

After incision of a femoral or brachial artery a catheter is passed into the aorta and advanced to a predetermined site, or into a main branch by means of an electromagnet attracting a chain of small steel links at the catheter tip. In 7 attempts at renal artery visualization 6 were satisfactory.

The author suggests that occasional arterial spasm and the complicated electromagnetic equipment are drawbacks, but insists that the method is safe and reliable.

SCHWEDEL

SURGERY AND CARDIOVASCULAR DISEASE

Kirklin, J. W., Daugherty, G. W., Burchell, H. B., and Wood, E. H.: Repair of the Partial Form of Persistent Common Atrioventricular Canal. So-called Ostium Primum Type of Atrial Septal Defect with Interventricular Communication. Ann. Surg. **142:** 858 (Nov.), 1955.

The authors describe a case of persistent common atrioventricular canal defect that was successfully treated by surgery. This type of atrial septal abnormality is one in which the lower part of the atrial septum is absent and the interatrial communication lies immediately above the ventricular septum. It is attributable to lack of fusion of the components of the atrial septum to the atrioventricular endocardial cushions.

The patient operated upon was a 27-year-old white woman who complained of progressive dyspnea, fatigue, and mild chest pain on exertion. Fluoroscopic and x-ray examination revealed enlargement of the pulmonary trunk, pulmonary arteries, and right ventricle, with increased pulsation of the pulmonary arteries. Catheterization demonstrated arterialization in the right atrium, while dye-dilution curves indicated a large left-to-right shunt.

By means of the atrial well of Gross, the right atrium was entered and a piece of polyvinyl was sutured into the defect. The postoperative course was uneventful. Study by cardiac catheterization 4 months after surgery showed that the defects in both the atrial and ventricular septa were completely closed and the heart was hemodynamically normal.

ABRAMSON

Poth, E. J., Johnson, J. K., and Childers, J. H.: The Use of Plastic Fabrics as Arterial Prostheses. Ann. Surg. **142:** 624 (Oct.), 1955.

The authors discuss the use of a multiple-layered arterial prosthesis, made from inert synthetic fabrics and consisting of an inner tube and an external "wrap around." They believe that the immediate results obtained with inert synthetics are satisfactory and greatly simplify arterial replacement. However, they realize that it is difficult to assess the ultimate value of such an approach.

The authors conclude that clinical use of the inert synthetic fabrics for arterial prostheses is as equally justified as that of arterial homografts.

ABRAMSON

Crawford, E. S., and DeBakey, M. E.: The By-Pass Operation in the Treatment of Arteriosclerotic Occlusive Disease of the Lower Extremities. Surg., Gynec. & Obst. **101:** 529 (Nov.), 1955.

The authors discussed the various surgical approaches to the treatment of segmental thrombosis of the main arterial channels in the lower extremities and described the method of by-pass of the diseased area with a graft. The latter operation was attempted in 40 extremities, and in 37 the blood flow was successfully re-established. This was determined by arteriography and the return of palpable pulses distal to the block.

Following operation, intermittent claudication and rest pain were relieved, and ulcers became painless and healed rapidly. All the grafts remained patient for periods up to 18 months.

The authors concluded that the by-pass procedure, owing to its simplicity in concept and application, is the most effective in achieving the desired objectives and is associated with the fewest disadvantages.

ABRAMSON

Murphy, T. O., Gott, V., Lillehei, C. W., and Varco, R. L.: The Results of Surgical Palliation in 32 Patients with Transposition of the Great Vessels. Surg., Gynec. & Obst. **101:** 541 (Nov.), 1955.

The authors analyzed a group of 114 patients with complete transposition of the pulmonary artery and aorta and found that only 4 per cent were alive at 7 years of age; 78 per cent expired during the first year of life. If any attempt at surgical intervention is to be carried out, it must be done at an early age and at the first signs of deterioration of the general condition of the patient.

The authors presented the results of attempts at surgical palliation in 32 patients with complete transposition. In each case associated congenital defects were present. Among the types of surgical procedures attempted were establishment of a venous shunt to the right atrium by means of transplanting the right pulmonary artery and

systemic arterialization of the pulmonary vascular bed. Of the 32 patients operated upon, 7 survived.

ABRAMSON

Riberi, A., Shumacker, H. B., Jr., Siderys, H., and Grice, P. F.: Experimental Repair of Ventricular Septal Defects under Hypothermia. Surg., Gynec. & Obst. **101:** 592 (Nov.), 1955.

Repair of an experimentally produced ventricular septal defect was performed upon dogs cooled to a body temperature of 30 C. by immersion in a bath of ice and water. Considerable difficulty was encountered because of adhesions between the heart and pericardium resulting from the previous procedure. Eight of the dogs survived successful repair of the defect, while the remainder died during or immediately after the operation.

In another group the defect was made and then repaired during the course of 1 operation. However, the closure of the defect was more difficult than in the first group. The authors expressed doubt as to whether the approach described was applicable for clinical repair of ventricular septal defects.

ABRAMSON

Baden, H.: Semi-Continuous Left Atrial Pressure Measurements During Mitral Valvotomy. Thorax **10:** 237 (Sept.), 1955.

During 16 operations for mitral stenosis, repeated measurements were taken in the left atrium by means of an indwelling cardiac catheter. Plotting of the obtained values in a pressure-time system demonstrated that the left atrial pressure in the pre- and postvalvotomy period varied considerably, and rendered a single pressure measurement before and after valvotomy valueless for an assessment of the effect of the operation on left atrial pressure. In 1 of 5 successful valvotomies a slight overlapping of pre- and postvalvotomy pressures was present. In 2 less successful valvotomies an unmistakable decrease of pressure was recorded. It must be concluded that serial measurements of the left atrial pressure add little or nothing to the surgeon's assessment of the result. The factors that may influence the atrial pressure during operative conditions were discussed. The left atrial pressure had a direct relation to the heart rate in a few cases in the prevalvotomy period; no relation was demonstrable in any case in the postvalvotomy period. No other known factor bore any clear relation to the left atrial pressure, and the unpredictable course of the pressure curves cannot be explained at the present.

BERNSTEIN

Crawford, E. S., DeBakey, M. E., Creech, O., and Cooley, D. A.: Use of Arterial Homografts in 90 Peripheral Arterial Lesions. Texas J. Med. **51:** 700 (Oct.), 1955.

By using arterial homografts, segmental arterial lesions can be treated effectively by a direct surgical approach with restoration of arterial continuity and normal function. This form of surgical therapy was employed in 67 arteriosclerotic occlusions, 28 of which involved the iliac and 39, the femoral artery. Short occlusions were excised completely and replaced by the graft. In the majority of cases the occlusion was simply bypassed by anastomosing the graft to the host artery above and below the lesion. All iliac occlusions and 87 per cent of the femoral occlusions were treated successfully, and the results obtained were superior to all other forms of therapy. Ten peripheral aneurysms in 9 extremities were excised and the defect bridged with homografts. Two of these failed because of technical errors. In the treatment of 20 arteriovenous fistulas, homografts were required in 4, while the others were treated by simple excision and suture repair. The circulatory changes were corrected in all, and the grafts have remained patent. Arterial homografts were used to bridge 10 traumatic defects of major peripheral arteries with successful restoration of circulation in all.

BERNSTEIN

Bruzzone, P. L., and Guglielmini, G.: The Left Auricular Appendage, Observations During Surgery for Mitral Commissurotomy. Arch. sc. med. **100:** 455 (Dec.), 1955.

The anatomic variations of the left auricular appendage observed in 700 operations for mitral commissurotomy are reported. Nonpathologic variations in shape and volume are described, and especially the stricture at the union with the atrium proper and the very small appendage. A large atrium is usually associated with mitral regurgitation. The atrial wall may be unusually thin or calcified. Other pathologic changes described are pericardial adhesions, the frequent endocavitary thrombosis, and posterior displacement of the atrium. In re-operation for recurrence of stenosis, entry in the atrial cavity through the auricular appendage may be impossible.

CALABRESI

Baffes, T. G.: Adaptation of Homologous Aortic Grafts for Surgical Correction of Infantile Coarctation of the Aorta. Surgery **38:** 486 (Sept.), 1955.

Use of homologous aortic grafts in the treatment of adult coarctation of the aorta is a well-established procedure. Infantile coarctation, on the other hand, often cannot be corrected by present surgical procedures. It consists of a relatively long segment of partial obliteration involving the distal aortic arch, may involve 1 or both of the carotid vessels, and frequently involves the left subclavian artery, causing the characteristic manifestation of hypertension limited to the right upper extremity. Occasionally, a large patent ductus arteriosus supplies blood to the descending aorta. Local excision of these long segments of infantile coarctation is usually impossible. In most cases, the condition is not compatible with long life.

In a review of all operative and autopsied cases entering the Childrens' Memorial Hospital of Chicago since 1940, 105 cases of coarctation of the aorta were collected. Fifty-nine cases were amenable to excision and end-to-end anastomosis. Twenty-six cases had long infantile coarctation of the distal ⅔ of the aortic arch, and aortic grafts to shunt the aortic stream around the coarctation into the descending thoracic aorta could have been used. In 43 mongrel dogs the technical aspects of the proposed operation were developed. The ascending limb of the aortic arch was anastomosed to the descending limb with a homologous aortic graft, and then the arch was ligated between the sites of anastomosis. The last 12 dogs were operated upon without any immediate or delayed operative mortality. A 6-month postoperative follow-up was completed. Twelve dogs with obligatory shunts through homologous grafts were available. Two grafts were examined after 1 month, 5 after 3 months, and 5 after 6 months. All were widely patent and successfully carried the entire aortic stream around the obstruction in the distal aortic arch. All had been well revascularized by adhesions from the adjacent pericardium, pulmonary artery, and left lung. Calcium had been laid down in the walls of some of the older grafts, and their intima showed evidence of furrowing. There was, however, no evidence of intimal destruction or aneurysmal dilatation.

MAXWELL

Borrie, J.: Mitral Insufficiency: Experimental Circular Suture around the Atrioventricular Ring. J. Thoracic Surg. **30:** 687 (Dec.), 1955.

The fibrous ring supporting the mitral valve can be effectively narrowed by passing a double floss-silk circular suture around it. In the initial 18 experiments, where the suture lay below the left coronary artery, although 11 animals recovered from operation, 3 died from acute coronary occlusion. In 9 subsequent experiments, where the suture lay above the left coronary artery, all animals recovered. The resulting narrowing and thickening of the A-V ring did not interfere with the action of the mitral valve cusps and chordae tendineae.

It is concluded that this method may well prove to have a real place in the surgical correction of mitral insufficiency, especially in patients with a widely dilated mitral valve ring. Cardiotomy would be the first step to assess the pathologic type of mitral insufficiency. Thereafter, the circular suture would be inserted, and the degree of tightening judged by intracardiac palpation.

MAXWELL

Dodrill, F. D., Lui, A., Nyboer, J., Rippingille, E. V., and Hughes, C. H.: The Arterialization of Blood as it Applies to the Mechanical Heart-Lung Apparatus. J. Thoracic Surg. **30:** 658 (Dec.), 1955.

A means of arterializing the blood during a total bypass is presented. The basic principle is the passing of O_2 and CO_2 through a metallic plate with holes of 10 μ in diameter. This produces tiny bubbles that come in contact with the venous blood by a swirling action. Instead of using 100 per cent O_2, which removes excess CO_2, the authors used 98 per cent O_2 and 2 per cent CO_2. The addition of 2 per cent CO_2 to the O_2 keeps the CO_2 at essentially a normal level and, therefore, the pH is not excessively altered.

Studies on dogs utilizing the apparatus described with total bypass for periods of up to 30 min. revealed normal arterial O_2 saturation, CO_2 content, pH of arterialized blood, blood counts, platelet counts, and fragility tests. The recovery rate with a total bypass in the dog with the right ventricle open for 30 min. was 75 per cent.

MAXWELL

Leary, H. J., Kelley, G. E., and Gregg, R. O.: Branched Arterial Homografts. Surgery **38:** 476 (Sept.), 1955.

The fate of branched arterial homografts following replacement of the terminal aorta and its 3 major branches was determined in 35 dogs. The abdominal aorta, just distal to the renal arteries and approximately 6 to 8 cm. of each iliac artery as well as 1 cm. of the middle branch (the abdominal aorta in dogs divides into 3 branches), was resected from donor dogs within 4 hours of death. Three methods of preserving the homografts were employed. 1. The technic described by Gross with a modified Tyrode's solution, penicillin, streptomycin, and homologous dog serum was used in the first group of dogs. These grafts were stored at 4 C. for varying periods of time, but not over 21 days. 2. Homografts were frozen quickly in a bath of dry ice and alcohol and stored at −70 C. from 7 to 99 days. 3. Homografts were prepared by freeze-drying and then Carrel suture of no. 5-0 silk was used. Plastic shunts to maintain circulation or anticoagulants were not used. All dogs were examined post mortem. The dogs were followed from 1 to 536 days.

Satisfactory grafts were obtained in 7 of 11 "Tyrode" grafts, 4 out of 13 frozen grafts, and 3 out of 10 lyophilized grafts. The straight segments of the grafts were patent in 10 of 11 "Tyrode" grafts, in 8 of 13 frozen grafts, and in 6 of 10 lyophilized grafts. Calcification occurred in 3 of the frozen grafts. Atrophy to a marked degree occurred in 3 of the frozen grafts and in 1 of the lyophilized grafts. On the basis of this study, preservation of homografts in modified Tyrode's solution was superior to preservation in the frozen state or after lyophilization.

MAXWELL

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SECOND CEREBRAL VASCULAR DISEASE CONFERENCE: JANUARY 16–18

Approximately 60 distinguished foreign and American participants will attend the Second National Conference on Cerebral Vascular Diseases at Princeton, N. J., Nassau Tavern, January 16–18. Irving S. Wright, M.D., New York, Conference Chairman, announced that attendance at this gathering, which will follow the pattern set by its predecessor held in 1954, is by invitation only.

The American Heart Association acts as one of the sponsors. Grants from the National Heart Institute and the Albert and Mary Lasker Foundation will help to underwrite the expenses.

The conference will be conducted as a series of round table discussions which will be transcribed and published as Transactions. These will be made available to the medical profession.

Among the disciplines to be represented at the conference will be pathology, brain chemistry, physiology, blood coagulation studies, neurology, neurosurgery, psychiatry, electroencephalography, and studies in the field of hypertension, atherosclerosis and rehabilitation.

NEW OFFICERS OF ASSOCIATION, COUNCILS AND SECTIONS

Edgar V. Allen, M.D., Senior Consultant in Medicine at the Mayo Foundation, Rochester, Minn., has assumed his duties as President of the American Heart Association. Dr. Allen succeeded Dr. Irvine H. Page, Cleveland, to the Presidency at the Annual Meeting of the Association in Cincinnati in October.

Robert W. Wilkins, M.D., Associate Professor of Medicine, Boston University, was chosen as President-elect.

Newly elected as Vice Presidents were: Francis L. Chamberlain, M.D., San Francisco; Irving B. Hexter, Cleveland; and Sylvester L. Weaver, Jr., New York.

The following were re-elected as Vice Presidents: William H. Bunn, M.D., Youngstown, Ohio; S. DeWitt Clough, Chicago; Mrs. Preston Davie, New York; Eugene B. Ferris, M.D., Atlanta; Louis E. Martin, M.D., Los Angeles; David D. Rutstein, M.D., Boston. Berkeley D. Johnson, New York, was re-elected Treasurer.

The Association's Councils and Sections have chosen the following officers:

Scientific Council: As retiring President, Dr. Irvine H. Page, Cleveland, automatically becomes Chairman of the Scientific Council. Eugene A. Stead, Jr., M.D., Durham, N. C., Vice Chairman; George C. Griffith, M.D., Pasadena, Cal., Secretary.

Section on Basic Science: Hymen S. Mayerson, M.D., New Orleans, Chairman; James V. Warren, M.D., Durham, N. C., Vice Chairman; Lysle H. Peterson, M.D., Philadelphia, Secretary.

Section on Circulation: Edgar A. Hines, M.D., Rochester, Minn., Chairman; William Goldring, M.D., New York, Vice Chairman; Grace M. Roth, Ph.D., Rochester, Minn., Secretary.

Section on Clinical Cardiology: William P. Thompson, M.D., Los Angeles, Chairman; Hugh Hussey, M.D., Washington, D. C., Vice Chairman; Francis F. Rosenbaum, M.D., Milwaukee, Secretary.

Section on Cardiovascular Surgery: Frank Glenn, M.D., New York, Chairman; Robert Gross, M.D., Boston, Vice Chairman; Jere W. Lord, M.D., New York, Secretary.

Officers for the *Council for High Blood Pressure Research* were scheduled for election at the Council's Annual Meeting in Cleveland, November 30–December 1.

Council on Community Service and Education: Ray E. Trussell, M.D., New York, Chairman; Oglesby Paul, M.D., Chicago, Ill., Vice Chairman.

Council on Rheumatic Fever and Congenital Heart Disease: Maclyn McCarty, M.D., New York, Chairman; Currier McEwen, M.D., New York, Vice Chairman.

REPRINTS OF ARTICLE ON ANTICOAGULANT THERAPY

A two-part article, "Anticoagulant Therapy," has been reprinted by the American Heart Association from the July 1956 issue of *The American Journal of Nursing*. It contains information useful to nurses and social workers.

Charles D. Marple, M.D., Medical Director of the American Heart Association, prepared the first part of the article dealing with medical aspects, while Miss Marie J. McIntyre, instructor in public health nursing, Russell Sage College, School of Nursing, Troy, N. Y., provided the second part, dealing with nursing care. Reprints are available from affiliated Heart Associations or from the American Heart Association. (Single copies free; $1.95 per 100).

GUIDE FOR PARENTS OF CHILDREN WITH RHEUMATIC FEVER ISSUED

A booklet directed especially to parents of children with rheumatic fever may now be obtained by physicians from the American Heart Association and its affiliates.

The new illustrated booklet, "If Your Child Has Rheumatic Fever," is also of interest to social workers and public health nurses who are required to interpret the physician's instructions to parents. Adapted from a publication issued by the Children's Bureau of the U. S. Department of Health, Education and Welfare, the 19-page brochure provides useful information for reinforcing the physician's advice and may be distributed by physicians to the parents of young rheumatic fever patients.

"If Your Child Has Rheumatic Fever" discusses the problem of caring for young patients during the acute and convalescent phases of the disease and emphasizes the importance of measures to prevent return attacks. (Single copies free: $3.50 per 100 booklets.)

The new booklet is the latest in a series of American Heart Association publications and visual aids bringing information about rheumatic fever and rheumatic heart disease to physicians and laymen.

ASSOCIATION RECEIVES PUBLIC RELATIONS AWARD

The American Heart Association has received an Achievement Award from the Public Relations News.

The award described as the "highest recognition in the public relations field," is presented each year to ten organizations judged to have made outstanding contributions to professional and management public relations progress.

The award, accepted for the Association by Dr. Irvine H. Page, retiring President, was conferred at the Annual Dinner in Cincinnati. The Association was commended "for formulating and executing a public relations program which disseminates information about heart disease, thereby saving countless lives and giving hope for happy and constructive living to those afflicted with the malady."

MEETINGS CALENDAR

December 26–31: American Association for the Advancement of Science, New York. Dr. Allan D. Bass, Department of Pharmacology, Vanderbilt University School of Medicine, Nashville 5, Tenn.

January 16–18: Conference on Cerebral Vascular Diseases, Princeton, N. J. Irving S. Wright, M.D., Cornell Medical Center, 1300 York Ave., New York 21, N. Y. (By invitation.)

January 16–19: Neurosurgical Society of America, Palm Springs, Calif. Frank P. Smith, 260 Crittenden Blvd., Rochester 20, N. Y.

January 25: American Federation for Clinical Research, (Southern Section) New Orleans. Samuel P. Martin, M.D., J. Hillis Miller Health Center, University of Florida College of Medicine, Gainesville, Fla.

January 30–31: American Federation for Clinical Research (Western Section), Carmel, California. Sherman M. Mellinkoff, M.D., Department of Medicine, School of Medicine, University of California Medical Center, Los Angeles 24, Calif.

February 4–6: American Academy of Allergy, Los Angeles. Francis C. Lowell, 65 E. Newton St., Boston, Mass.

February 8–9: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Dr., Chicago 6, Ill.

March 4–6: National Biophysics Conference, Columbus, Ohio. Samuel A. Talbot, Department of Medicine, Johns Hopkins Hospital, Baltimore.

March 25–28: American Academy of General Practice, St. Louis. Mr. Mac F. Cahal, Volker Blvd., Kansas City 12, Mo.

ABROAD

January 3–6: International Congress of Union Against Tuberculosis, New Delhi. Union Against Tuberculosis, 66 Blvd St., Michel, Paris 6e.

February 24–28: Diennial International Scientific Congress, International College of Surgeons, Mexico City. Dr. Max Thorek, International College of Surgeons, 850 Irving Park Rd., Chicago.

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